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ELSEVIER

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Foreword

I lost a friend my age to osteosarcoma when I had barely turned twenty. Tim's death imprinted me with the horrors of malignant disease. About 5 years later, in 1979, my first patient as a new graduate was a basset hound with lymphosarcoma. Very little was known then about treating osteosarcoma, lymphosarcoma and indeed most cancers in people or animals. Sue Cotter had not written about the efficacy of COP and all that was known was that my basset was going to die of this disease just as Tim died of his.

We must be able to do more.

Since those days, my life has been dedicated to treating cancer in animals and clinical cancer research. I am privileged to be the first surgical oncologist to come through Colorado State University's surgical oncology fellowship. I have worked with amazing and talented people and have experienced intelligence, enthusiasm, courage and determination in people who have inspired me and in those I have inspired.

Susan North and Tania Banks rank highly in this group of such wonderful people and the book they have produced is inspirational. This text provides veterinarians with the opportunity to make a big difference. Patients with lymphosarcoma, osteosarcoma and indeed most cancers now have chances. Chances for extended periods of excellent quality of life are now real probabilities. For many cancers there exists the possibility for cure. Early detection, accurate diagnosis, staging and appropriate first-line treatments are the keys, together with a sound understanding of the cancer being treated. Susan and Tania provide the veterinary community with this excellent text to guide towards providing the best care for small animals with cancer, practically, ethically and with the utmost respect for their quality of life and for the quality of life of those who love them.

We are able to do more.

Rodney C Straw BVSc DACVS

Preface

The science of veterinary oncology continues to grow, with ever-increasing numbers of clients seeking treatment for their dogs and cats once a diagnosis of cancer has been made. The purpose of this book is to provide an accessible source of information to practising veterinary surgeons with an interest in oncology and to veterinary students, interns and residents who will soon be dealing with patients with cancer. We hope that to some degree we have kept this an informal book, not too heavily filled with references, but rather injected with some of our personal experiences and approach to the veterinary patient with cancer, always remembering the importance of compassion and understanding in dealing with individual clients and patients. In many cases oncology is not an exact science as each manifestation of cancer is as unique as the individual who suffers from it and we have endeavoured to emphasise throughout this book the importance of attention to the individual, ability to perceive potential problems and adjust treatment as necessary. There is often more than one option that can be followed and in some instances, such as the management of mast cell tumours, there continues to be differences of opinion as to the optimal treatment. To the practising veterinary surgeon this can be frustrating, and to the oncologist challenging, as we strive to give the best possible care to our patients.

The layout of the book provides an overview of cancer biology; this is meant to stimulate interest in the basic science rather than an in-depth discussion. We both hope that after reading these introductory chapters the reader will be motivated to pursue additional texts and articles. A systems approach has been used to describe the individual tumours seen most commonly in our companion animals; sometimes it was difficult to know exactly where to include a particular tumour and cross-referencing between chapters was necessary. Throughout this book we have emphasized the principles of oncology that should be applied to every veterinary patient: good history and physical examination, establishment of an appropriate minimum database, the importance of biopsying and staging malignancies, pre-planning of treatment, and interaction with, and referral to, specialists when appropriate to ensure the best possible outcome for the patient. We have also sought to show that for the best management of cancer patients an interdisciplinary approach is required and the best outcomes occur when surgeons and medical/radiation oncologists work together from the very beginning. These specialists also need the support of imaging and internal medicine specialists. Dedicated centres now exist that bring together this specialist knowledge, along with the sophisticated equipment required for advanced treatments such as radiation therapy. We hope that by showing what can be done in such centres the collaboration between front-line veterinary surgeons and specialists will continue to develop.

We have both found it extremely challenging to sit down and write this book. It was difficult to always know what to include and what to leave out, but we have endeavoured to cover the most frequently encountered tumours in depth and at the same time to mention those seen less frequently to increase awareness of 'newly' emerging cancers such as histiocytic sarcoma.

Our patients continue to be an inspiration to us as is the dedication of their human companions. We learn so much from them on a daily basis and we hope that this book dedicated to all our patients will be a valuable guide to front-line veterinary surgeons in their quest to provide ever-improving care and quality of life for these animals. The greatest reward is seeing the wagging tail of a patient as they race down the corridor to go home.

Acknowledgements

To all those clients who put their trust in me with the many thousands of dogs and cats I have met and cared for over the years, driving me on to constantly improve my understanding of veterinary oncology so that I can provide better treatment for those who follow.

To cancer that provides me with a constant challenge that has stimulated my thirst for knowledge for over 30 years, and finally to Malcolm and my current dogs "Rodin" and "Byron", quick to forgive and always there for me.

Susan North

To Rodney Straw and Susan North for their constant support and inspiration. To the veterinarians and veterinary students who continue to strive to provide better and better treatments for pets with cancer, and to those loving owners and their beloved pets who seek our help.

Tania Banks

The human–animal bond and why veterinary oncology is important

Introduction

The purpose of this book is to provide a basic understanding of veterinary oncology as it is today. It is not meant to provide an exhaustive text and a 'recipe' for every cancer, but rather to present the principles on which we can all build to improve the level of cancer care we can offer to our patients.

Why is that important?

Cancer in companion animals is a leading cause of death. The prevalence of cancer is increasing and a number of factors are contributing to this increase, in part reflecting the ageing of our canine and feline populations (Cooley et al 2003, Lord et al 2007). Cancer is predominantly a disease of middle aged to older patients, and as our ability to control other diseases, improve nutrition and practise good preventative medicine has resulted in our companion animals living longer, then it stands to reason that the incidence of cancer will also increase.

It is important because, to many individuals, the dog or cat with whom they share their home and lives is an integral member of the family and whatever decision they ultimately make as to treatment is made with the best intentions for the animal in question. It is our responsibility as medical professionals to provide the facts and the options to our clients so that they can make an informed choice.

As medical professionals it is our responsibility to provide the best care for our veterinary patients in respect to cancer diagnosis and treatment and in doing so acknowledge the strength of the human–animal bond. The recognition of the importance of companion animals to the emotional wellbeing of human beings is now well known – not only do they 'complete the family' and provide valuable lessons to children about the responsibility of relationships, they provide companionship and in some cases a valuable link to the outside world when they help us as guide dogs, hearing dogs, dogs trained to assist the disabled, in Search and Rescue and many other fields. Dogs have been shown to improve quality of life and reduce stress, and studies have shown that people living alone with a dog or cat for a companion have a better quality of life than those without. These significant benefits to our lives mean that the relationship people have with an animal may be of greater or equal importance to them as their relationships with other people. Clients who have invested a great deal of love and care into an individual do not find it acceptable to be told, 'Your dog/cat has cancer and should be put to sleep'. They do not consider the individual as a disposable item easy to replace, but rather want to know what can be done to help the dog/cat standing before you.

What can we do to improve care for our patients?

Prevention is better than cure. In the field of human oncology we encounter a great deal of information on preventing cancer and the role that life-style choices contribute to its development (Soerjomataram et al 2007). We are all aware that smoking is linked to lung cancer, excessive exposure to sunlight with melanoma and Western 'high-fat' diets with breast and colon cancer. In turn, the incidence of many cancers can be prevented in our veterinary patients. Early ovariohysterectomy not only eliminates neoplasia of the uterus and ovaries, it also significantly reduces the incidence of mammary carcinoma. Neutering males eliminates testicular cancer. Counselling clients on neutering early is an easy and important part of preventative medicine.

Early diagnosis improves prognosis in many instances. In human oncology screening tests are available for the more commonly seen cancers, mammograms for breast cancer, cervical smears for cervical cancer, etc. We can apply this principle easily to our veterinary patients without incurring huge costs. The simplest and often the most effective test is a good physical examination to include a rectal exam. Routine rectal examination on dogs of greater than 5 years of age would allow for early detection of canine anal sac adenocarcinoma, thus reducing the need for extensive surgery and improving potential outcome for the patient. It also allows for early detection of prostatic neoplasia, particularly in neutered dogs.

Many cancers in veterinary oncology are detected only when they are very advanced. Part of this is because our patients cannot tell us when something just isn't right, but also because they will carry on appearing relatively normal to the client but just 'slowing down'. Many cancers are occult and it may be some time before an obvious abnormality becomes apparent. Offering good diagnostic evaluations early will improve prompt detection of cancer and the opportunity to treat patients early; this in itself will improve survival times for many patients. The veterinary surgeon needs to be constantly thinking about underlying causes for the simplest of presenting signs:

- haematuria in a middle-aged dog (could it be bladder cancer?)
- seizures in an older dog (could it be a brain tumour?)

- unilateral nasal discharge or epistaxis in either a dog or cat (could it be a nasal tumour?)

and so the list goes on. Rational evaluation of the patient and considering the possible differentials for each presenting clinical sign, taking into account the signalment and circumstances of each patient, will automatically result in earlier detection and better treatment.

The next step is to involve specialists early. The 'shelling out' of tumours can present significant problems when it comes to follow-up therapies such as radiation. Irradiating a scar without having seen the original tumour can be difficult and the main cause of treatment failure in these cases is geographic miss. Consultation with the client for early referral so that the same team carries out surgery and adjunctive therapy greatly improves the success of treatment. In some cases clients will decide against referral but that should be their choice.

The science of veterinary oncology is fascinating for those involved in it. As our knowledge of canine/feline genetics increases, the opportunities to participate in collaborative studies on comparative oncology with our 'human counterparts' continue to grow. This means potentially new treatments will become available to our patients sooner than in the past. By working together human and veterinary oncologists can help each other. Many of the naturally occurring cancers in our companion animals mirror similar conditions in people, but because of the shorter life span data can be accumulated much quicker. One example of a canine cancer that behaves in a biologically similar way to a human cancer is appendicular osteosarcoma, an excellent comparative model for paediatric osteosarcoma.

What about treatment options?

The decision to treat is made by the client and to do that they need to know what the options are. Do not second guess what they might want or be able to afford. Discuss treatment honestly, including the expected benefits and potential problems. Many clients are emotionally vulnerable because of their deep attachment and trust you to guide them. It is a great responsibility to ensure that the correct decisions are made for each client and patient and that no other factors influence decisions except the wellbeing of the patient. With any cancer, treatment should start as soon as possible. It is therefore important not to delay, especially in cases where the tumour may be growing quickly (mast cell tumour) or the patient could go from being clinically well to unwell very quickly (lymphoma).

What about palliative care?

For terminally ill human cancer patients the phrase 'palliative care' has become part of a humane approach to cancer treatment. Eventually, for the majority of human patients with cancer, treatment fails; options are exhausted and all that can be done is to keep the patient as comfortable as possible.

In veterinary medicine the situation is slightly different in that we have the option of euthanasia. For many clients this can be an agonizing decision to make and the concern is to time it exactly right. To get this decision wrong can result in feelings of guilt and recrimination and the veterinary surgeon is the professional to whom they turn for advice. In some patients quality of life can be maintained with palliative care options that usually involve controlling clinical signs or pain. Perhaps the most obvious example of this is palliative radiotherapy for dogs with inoperable appendicular osteosarcoma. It is important to remember that for the majority of patients amputation is the treatment of choice and even large dogs such as Rottweilers and Mastiffs can do well after surgery, if you chose your patients carefully. In those patients with other orthopaedic issues or metastases, radiotherapy can offer a great deal of relief from pain and is effective palliative therapy. General pain relief will, in many cancer patients, give them extra quality time, but eventually these options provide no real improvement and the gentle task of discussing euthanasia becomes inevitable.

How to deal with euthanasia and the grieving client?

Providing support to the client is part of our professional responsibility; however, we as individuals are not qualified grief counsellors and dealing with the emotions that may be unleashed at such a time can be emotionally draining, particularly when it occurs over and over again. It is important when dealing with grieving clients not to become overwhelmed, as this will reduce your ability to function and ultimately lead to professional 'burn-out'. In some cases it may be necessary to refer your client to a professional. However, in saying that, taking time to talk and making those last moments as special as possible is important. Euthanasia should never be rushed to fit in with a schedule; saying good-bye to a loved one takes time, and no matter what else the demands on our time may be, the individual grieving client must take precedence.

Home euthanasia can be very stressful for the veterinary surgeon but very comforting for the client as the surgery consulting room can appear too cold and clinical. When euthanasia is carried out at the surgery, try to make the surroundings as comforting as possible; the best option is to have a room set aside that can be used privately for euthanasia. Obviously this is not always possible, but a comfortable bed for the patient to lie on, and a discretely placed catheter so the client can easily hold and stroke the patient during the procedure, will help to make the atmosphere less clinical. Always offer them time to be alone with the departed if that is their wish. A few moments of sympathy can go a long way to alleviating the anguish that can be felt at such a time.

The management of the veterinary patient with cancer can be immensely rewarding as well as extremely sad. Many patients can be cured; many cannot, but the bond that can be established between the veterinary professional and the client during the months to years of treatment and aftercare is without doubt something special.

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CHAPTER 2

An introduction to the principles of tumour biology

Understanding the biology and genetic basis of cancer is imperative to improving our ability to provide effective treatments. This is a rapidly expanding field of knowledge and the purpose of this chapter is to introduce you to the existing level of understanding and the principles on which current and future treatments are based. Those readers interested in the basic science are referred to more advanced texts.

Tumour development and growth

Cancer is a genetic disease involving damage to the DNA leading to uncontrolled cellular growth. We know that there are a number of environmental factors and chemicals that can lead to the development of cancer (Table 2.1), including ultraviolet light (squamous cell carcinoma), aflatoxins (liver cancer) and viruses (leukaemia and lymphoma). To be carcinogenic these agents must cause damage at the genetic level.

The two-step theory of tumour development

Current belief favours a two-step theory of tumour development. The first step involves exposure of the cell to the carcinogen, known as the 'initiator', and results in permanent alteration of the DNA. A long lag period may then occur and it can be months or years before the second step, known as promotion, allows the transformed cells to progress into a state of uncontrolled growth. The 'promoter' may be the same agent as the initiator, or may be a second agent including normal growth promoters or hormones. Once the initial events have taken place at the level of the DNA, changes in expression of regulatory genes lead to unrestricted growth and oncogenesis.

What are the characteristics of malignancy?

Rapid cell division is a characteristic of malignancy and growth occurs because the normal regulatory apparatus of the cells is defective – in other words, there is a breakdown in homeostasis at the molecular level. Tumour cells are further characterized by their independence from external mitogenic stimuli allowing sustained growth and by their ability to avoid antigrowth signals that would normally lead to terminal differentiation and the post-mitotic stage. Mechanistically this relies on the activation of cellular oncogenes (Table 2.2).

For a tumour to establish itself it must rapidly develop a blood supply and to do that angiogenesis is required (Kerbel 2008). The ability of a growing tumour to induce angiogenesis is essential for its sustainability. The actual process is complex and involves factors produced by both host and tumour. Angiogenesis is maintained by a number of positive and negative signals that include soluble mediators and their receptors (integrins), and adhesion molecules that are responsible for cell and matrix interactions (Moschos et al 2007). Angiogenic factors include vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

Before a tumour can be detected clinically it must have reached a certain size. For superficial tumours, this means that approximately 10^9 cells are present and the tumour has undergone up to 30 doublings. The growth fraction of a tumour is not constant but decreases exponentially with time. If a tumour becomes very large there may be a deceleration in growth because of reducing oxygenation and nutrition within the tumour, leading to senescence or cell death and necrosis. Large tumours with a small growth fraction are resistant to modalities such as radiotherapy and chemotherapy that require cells to be actively dividing.

A characteristic of cancer cells is immortality. In part this feature resides in the production of the enzyme telomerase. Telomeres are the terminal ends of the chromosome and in normal cells these are progressively difficult to replicate with progressive cell divisions (Raynaud et al 2008). In normal cells the telomeres are so short that eventually the cell is made senescent. Tumour cells, however, have the capability of maintaining their telomeres by the production of telomerase. Telomerase is the underlying cause of immortality in cancer cells and is therefore a common marker of malignancy and potentially a therapeutic target (Harley 2008).

The goal of cancer treatment is cure. However, that goal is often not achieved because of the ability of malignant cells to metastasize.

What is metastasis?

Metastasis is the capability of malignant tumours to spread to distant sites and there develop into new tumours. It is combating the capability of cancer cells to metastasize that remains the most challenging aspect of cancer therapy. Primary tumours can, in the majority of cases, be controlled by surgery, radiotherapy or chemotherapy, or a combination of these modalities, especially when the tumour is detected early (good physical examination and prompt diagnostics) and treated appropriately. Unfortunately, even with early removal of the primary tumour, it is the ability of cancer cells to spread throughout the body, a process that commences as soon as

Table 2.1 Examples of agents reported to be tumorigenic in companion animals

Agent	Neoplasm	Species
Cyclophosphamide	Bladder transitional cell carcinoma	Dog
Oestrogen	Mammary carcinoma	Dog
Testosterone	Perianal adenomas	Dog
Air pollution	Tonsillar SCC	Dog
Fracture/implant	Osteosarcoma	Dog
Ocular trauma	Intraocular sarcomas	Cat
Spirocerca lupi	Oesophageal sarcoma	Dog
External beam radiation	Osteosarcoma	Dog
UV radiation	Cutaneous SCC	Dog, cat
	Cutaneous haemangioma/ sarcoma	Dog
Papilloma virus	Oral SCC (papillary variant)	Young dogs
FeLV	Leukaemia/lymphoma	Cats
FeSV + FeLV	Fibrosarcomas	Young cats

FeLV, feline leukaemia virus; FeSV, feline sarcoma virus; SCC, squamous cell carcinoma.

Table 2.2 Selected oncogenes and their products

Class	Oncogene	Product
Class I: Growth factors	*sis*	Form of platelet-derived growth factor
Class II: Growth factor receptors	*erb-b*	Epidermal growth factor receptor
Class III: Intracellular transducers	Protein tyrosine kinases, e.g. *met*	Protein kinases that phosphorylate tyrosine residues
	Protein serine-threonine kinases, e.g. *mos*	Protein kinases that phosphorylate serine or threonine
	Ras proteins, e.g. *N-ras*	Guanine nucleotide-binding protein with GTPase activity
Class IV: Nuclear transcription factors	*myc*	Regulation of transcription

For a more detailed list of oncogenes and their products, see Calvo et al (2005).

the tumour has established access to the lymphatics and blood supply, that usually leads to treatment failure and remains the biggest challenge in the management of patients with cancer. Metastatic spread can occur early in the development of a malignancy, even before the tumour is detectable by current methods. The process by which cancer cells spread to secondary sites involves a number of steps as well as an intimate interaction between host and tumour, and is described as the metastatic cascade (**Figure 2.1**).

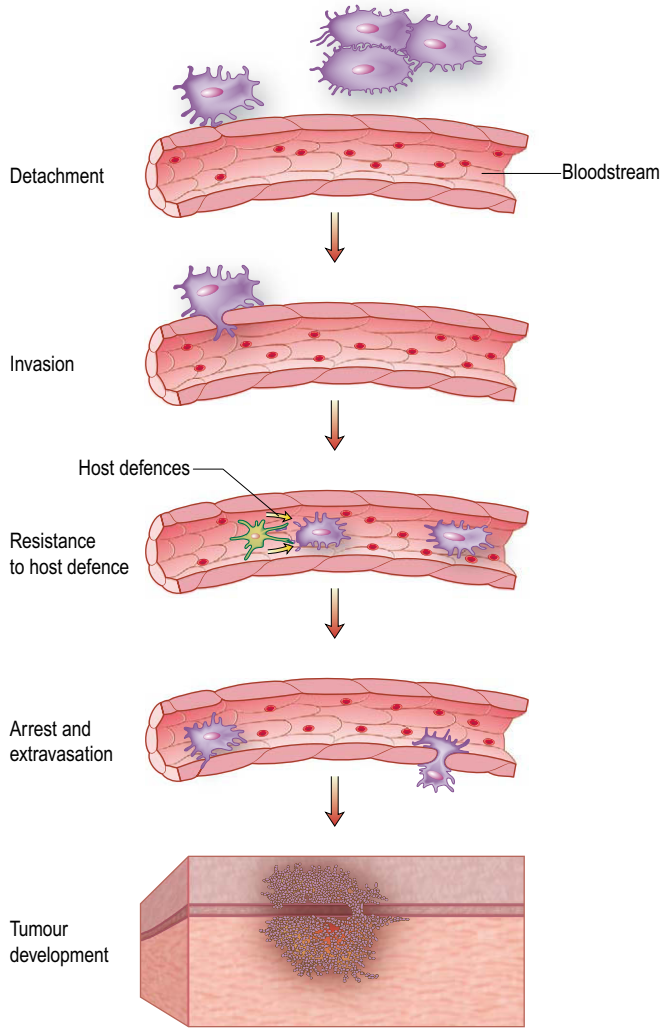

Figure 2.1 The metastatic cascade.

The metastatic cascade (for further details see Hill 1992)

Detachment and invasion

At the beginning of the metastatic process cells have to be able to mobilize themselves and break down normal tissue barriers to enable them to gain access to small blood vessels. This requires the production and release of proteolytic enzymes, growth factors, cytokines, etc. The cancer cells themselves produce some of these 'mediators of invasion', whereas others are produced by normal tissue components stimulated by the neoplastic cells.

Resistance to host defences

Studies in animals have shown that the majority of cells which gain access to the bloodstream die. This is between 90 and 99% and cell death is a consequence of both physical factors (e.g. shearing forces due to blood flow) and host immune defences, both specific and non-specific.

Arrest and extravasation

Arrestation at a secondary site involves an initial interaction with vascular endothelial cells, followed by digestion of the basement membrane by proteolytic enzymes, allowing tumour cells to leave the vasculature and establish metastatic foci. This means that tumour cells must be able to attach to the vascular endothelium and produce the necessary proteolytic enzymes to break down the extracellular matrix, allowing them 'entry' into the secondary site.

Establish new tumours

New tumours need to establish a good blood supply and therefore can either produce angiogenic factors themselves or induce normal cells to do this. The process of angiogenesis is basic to the establishment of new tumours.

Why do tumours have preferred metastatic sites?

We are constantly learning more about tumours at the cellular and molecular level but the observation that certain tumours metastasize to certain organs has been known for centuries and in 1889 Paget put forward his 'seed and soil' hypothesis. This has formed the basis of modern thinking about why tumours preferentially select certain organs. The concept of seed (receptors on the tumour cell surface) and soil (complementary receptors on the endothelium) explains the relationship that enables tumour cells to arrest in a particular vascular bed before extravasation. An important element of the 'soil' is the production of proteolytic enzymes and growth factors that allow tumours to become established and grow.

Strategies for preventing metastasis

Although it can be seen that tumour cells are vulnerable to attack at all stages of the metastatic process, overall it is an inefficient system, with the majority of cells dying before reaching secondary sites. It has been hypothesized that some cells possess a metastatic phenotype and these cells are actively selected for survival. Strategies to prevent the establishment of new tumour foci include targeting angiogenesis, enhancing the immune system to recognize and destroy neoplastic cells and inhibit the proteolytic enzymes required to break down the extracellular matrix, a prerequisite for metastasis.

What is the genetic basis for the development of cancer?

Oncogenes

The discovery of RNA tumour viruses (retroviruses) provided the first evidence for the role of genetic factors in the development of cancer. These viral oncogenes were shown to have transforming properties that lead to the development of tumours, e.g. rat sarcoma virus (v-*ras*). These viral oncogenes were then found to have cellular homologues, cellular oncogenes (c-*onc*). Changes in the level of oncogene expression results in malignant transformation.

Proto-oncogenes

These are cellular oncogenes that do not have the innate capacity to produce tumours but can be altered to do so. They are normal cellular sequences of DNA and their function is to regulate cell growth and differentiation in normal cells. The expression of cellular oncogenes is well regulated, allowing for normal cell function. Inappropriate activation of these genes can result in dysregulation of normal cell growth and differentiation, increasing the possibility of neoplastic transformation.

Changes in the level of oncogene expression result in malignant transformation. The products of proto-oncogenes consist of growth factors and their receptors, protein kinases, signal transduction genes and nuclear proteins (see Table 2.2).

For proto-oncogenes to contribute to malignant transformation the normal products of these genes must in some way be disrupted to result in uncontrolled cell division. A number of mechanisms by which this occurs have been found and include chromosomal translocations, gene amplification, point mutations and viral insertions (Table 2.3).

Tumour suppressor genes

In contrast to the changes in proto-oncogenes leading to stimulatory events resulting in tumour formation, changes in another class of genes can result in loss of inhibition leading to tumour formation. The latter class of genes is known as tumour suppressor genes, with *p53* and the retinoblastoma (*Rb*) genes being the most familiar.

p53

p53 is a tumour suppressor gene whose normal function is to restrict or inhibit cellular proliferation. The product of *p53* is able to move cells into arrest or apoptosis when the cell has received an 'insult' that may result in DNA damage. For this reason *p53* has been called the 'guardian' of the genome (Lane 1992). It is this ability of wild-type *p53* to regulate the transcription of a number of genes involved in cell cycle progression and apoptotic pathways that prevents the development

Table 2.3 Activation of proto-oncogenes

Mechanism	Oncogene	Example
Chromosomal translocations	c-*myc* placed under influence of immunoglobulin promoters and enhancers	Hodgkin's lymphoma (human)
	c-*abl* gene in Philadelphia chromosome	Chronic myelogenous leukaemia (human)
Gene amplification	*myc* proto-oncogene amplified	Neuroblastoma (human)
Point mutations	*ras* proto-oncogene, single base change	Many human tumours
Viral insertions	FeLV	FeLV–FeSV

FeLV, feline leukaemia virus; FeSV, feline sarcoma virus.

of potentially oncogenic mutations and tumour development. Mutations in *p53* can lead to a loss of function resulting in uncontrolled growth and tumour development. Despite *p53* being the most commonly inactivated gene in human cancers, the true relevance of changes in *p53* expression in veterinary cancers, although present, is currently unknown (Nasir et al 2000, 2001, Veldhoen et al 1998).

Viral oncogenesis in veterinary medicine

A number of viruses have been associated with tumours in domestic animals and include the DNA viruses and the retroviruses.

DNA viruses

Papilloma viruses are small DNA viruses whose replication cycle is linked with epithelial cell differentiation. Typically they give rise to benign papillomas in many species, including cattle, horses and dogs. Eventually they are eradicated by the immune system, usually over a 6-month period, and in dogs they are usually encountered in young animals. Occasionally they can become transformed into malignant growths.

Retroviruses

The most clinically relevant retrovirus is the feline leukaemia virus (FeLV) that has been associated with a large percentage of haemopoietic tumours (see Chapter 22) and FeLV–FeSV sarcoma complex.

FeLV is classified into three subgroups (Jarrett 1992):

- FeLV A: ecotropic and can only infect feline cells; this is the dominant form of the virus
- FeLV B: polytropic and is over-represented in cases of virally induced lymphoma in cats. It is thought to arise de novo from combination of FeLV A and endogenous sequences present in the genome
- FeLV C: also thought to arise de novo by mutation of the *env* gene in FeLV A; it is associated with the development of pure red cell aplasia in cats.

The association of FeLV with leukaemia and lymphoma, especially in young cats, is well known, and the development of vaccines, coupled with awareness of virus transmission, has resulted in a reduction of the 'typical' FeLV-positive cancer patient. Not all cats that develop lymphoma test positive for the virus but there is evidence to suggest that in certain cases virus may be involved as an initiating event before being eliminated by the immune system.

Acutely transforming viruses

This is a rare recombination between a cellular oncogene and the leukaemia virus. In approximately one-third of feline T-cell lymphomas the tumour contains a virus that is a hybrid of FeLV and the *myc* oncogene (Tsatsanis et al 1994). How this impacts on response to treatment is unknown.

Feline immunodeficiency virus (FIV)

This retrovirus is a lentivirus and typically has a slow incubation period. FIV has been associated with neoplastic disease in cats, especially lymphomas (Terry et al 1995). Neoplastic disease may result as a consequence of immunosuppression or possibly as directly oncogenic after viral insertion (Beatty et al 1998).

Inherited cancer

Familial cancers are known in humans and hereditary breast cancer is one of the best-known examples. Hereditary breast cancer accounts for only a small percentage of all breast cancer in women, and the most common inherited form arises from mutations in the regulatory *BRCA* tumour-suppressor genes. Inheritance of the deleterious mutation in *BRCA* is accompanied by up to 80% risk of developing breast cancer, 60% risk of developing contralateral breast cancer and up to 25% risk of developing ovarian cancer (Goldberg & Borgen 2006). As yet, no specific hereditary genes have been identified in companion animals and although there is much breed association with certain neoplasias, we have yet to find a cancer gene.

Further reading

There are many excellent texts available for readers interested in learning more about the genetic basis of cancer and many of the papers cited in the text are up-to-date review articles.

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Work-up of the cancer patient

When faced with a veterinary patient that may have cancer it is important to evaluate the patient in its entirety. The patient is very much more than a mast cell (MCT) or bone tumour and this should always be borne in mind when approaching the diagnostic work-up. What is appropriate will vary depending on the cancer that has been detected or the clinical signs exhibited by the patient. We all know the diagnosis of cancer is often made after the patient has presented with non-specific signs such as vomiting.

Physical examination

The value of good physical examination cannot be overemphasized. Early detection of neoplasia can, in many cases, give a good outcome. Thorough examination of lumps and bumps via fine needle aspirates (FNAs) can lead to the early detection of tumours such as MCT. Such tumours are much easier to remove when small and therefore will have potentially a better outcome for the individual and certainly reduce the requirement for extensive surgery or surgery and adjuvant therapy, or no possibility of surgery (**Figure 3.1**). If a lump is non-diagnostic on an initial FNA, do not discount it but alert the client to watch for any change and to come back if the lump grows or changes. Unfortunately, we see many veterinary patients where the initial evaluation was inconclusive and the lump had been left to grow into what may become an inoperable tumour, often because the original FNA was inconclusive and no follow-up was discussed with the client.

A complete physical examination should include routine rectal examinations for all dogs over 5 years of age; the early detection of tumours such as anal sac adenocarcinomas would dramatically affect the outcome with surgery, as too often the client goes to the veterinary surgeon because they have noticed a lump protruding close to the anus. By the time the tumour is so large as to be visible to the client it cannot be removed with adequate margins to guarantee complete excision and in some cases cannot be removed at all (**Figure 3.2**). The key to improving prognosis for many veterinary patients is both early detection and immediate action. Abnormalities on physical examination should always be followed up.

If an external lump is found on examination always palpate the draining lymph node for signs of enlargement; this is the beginning of the important process of staging.

Establishing a minimum database

The majority of animals with cancer are middle-aged to older and therefore it is just good medicine to establish a minimum database consisting of haematology, biochemistry and urinalysis. Other problems that may influence your treatment plan may be present, including use of cytotoxic drugs in patients with renal or liver disease. In some cases it is the abnormalities on blood tests that draw the clinician towards a diagnostic plan aimed at identifying neoplasia. For example, hyperglobulinaemia may be an indication of lymphoma or multiple myeloma. A leucocytosis may be indicative of a leukaemia. An elevated packed cell volume (PCV) may occur with renal carcinoma. Hypoglycaemia can occur due to an insulinoma. Anaemia, thrombocytopenia and granulocytopenia may indicate bone marrow disease. Increased alkaline phosphatase (ALKP) may occur with an osteosarcoma. Hypercalcaemia is a paraneoplastic syndrome that can occur with many cancers, but is seen most frequently with anal sac adenocarcinoma, lymphoma or multiple myeloma. However, it is important to remember that none of the above tests is diagnostic in itself for neoplasia and other medical reasons may underlie each clinical abnormality.

Urinalysis is also important – for example, renal function may be compromised with hypercalcaemia of malignancy. A low urine specific gravity (SG) may indicate polyuria/polydipsia (PU/PD), which can occur with many cancers. Haematuria may occur with urinary bladder neoplasia, a large number of patients with cancer have signs of proteinuria, and so the list goes on.

Clotting profiles are indicated in cancer patients prior to major surgery, particularly patients with suspected haemangiosarcoma, large mast cell tumours, haemolymphatic tumours, etc. Most patients with advanced neoplasia are in a state of chronic disseminated intravascular coagulation (DIC) but this is not always clinically relevant.

Cytology or biopsy

Ultimately, the nature of a tumour must be determined either by cytology or histology, and this is discussed in more detail in Chapter 4. Evaluation of draining lymph nodes by cytology, if appropriate, should be carried out at the same time. In many instances it is necessary to remove the sentinel node for histopathological evaluation.

Radiology

There are few instances when radiology does not have a role to play in the work-up of the veterinary patient with neoplasia. In some instances other imaging modalities are of greater

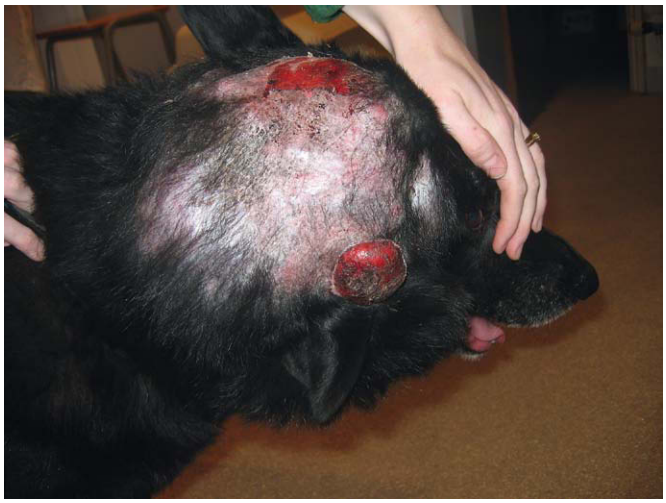


Figure 3.1 Large sarcoma on the head of a dog.

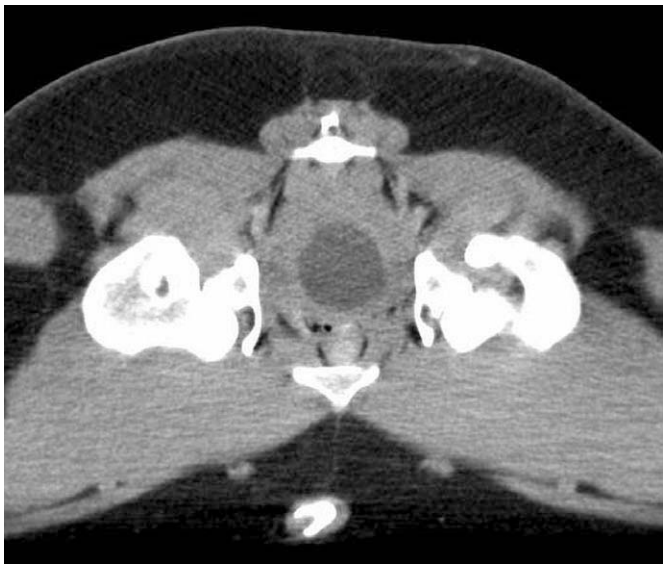


Figure 3.2 CT scan of a dog with extensive anal sac adenocarcinoma and sub-iliac lymph node metastases.

value and accuracy, e.g. ultrasound, CT/MRI (Table 3.1). Routine thoracic radiographs should be part of the minimum work-up for a middle-aged to older patient (you never know what you might find!). For patients with carcinomas/sarcomas, 'met' checks are indicated, consisting of at least right and left laterals, and a dorsoventral/ventrodorsal (DV/VD) view may also be helpful (**Figure 3.3**). CT is, however, the gold standard for checking for pulmonary metastases, so if CT is available this should be offered to the client (**Figure 3.4**).

Tumours such as mast cell tumours do not metastasize to the lungs but in an older patient it is advisable to obtain radiographs of the thorax to rule out other potential problems – for example, the incidental finding of another pulmonary mass. For patients with nasal tumours, intra-oral and frontal sinus films are indicated if CT/MRI is not available (**Figure 3.5**). Radiographs of oral tumours are indicated to evaluate the extent of bone destruction prior to surgery, but remember that no change will be seen on the radiograph until there has been ~40% bone loss. Radiographs (thorax and abdomen) are necessary to stage patients with lymphoma to evaluate internal lymph nodes etc. Abdominal radiographs are an important first test for a patient with palpable abdominal masses and are used to stage rectal tumours etc. by evaluation of the sub-iliac lymph nodes.

Routinely, ultrasonography is a more accurate diagnostic tool than plain radiographs and CT gives an accurate evaluation of the pelvic canal.

Contrast studies are valuable in the diagnosis of some gastrointestinal tumours where filling defects can be seen. Although contrast studies are still used to identify bladder tumours, ultrasonography has superseded these studies in many instances; however, urethral tumours are still diagnosed with contrast studies.

Table 3.1 Imaging the veterinary patient with cancer

Area of interest	Imaging of choice	Other imaging modalities
Jaw	CT	Radiographs
Skull, frontal sinus	CT	Radiographs, MRI
Nasal cavity	CT	Radiographs, MRI
Brain	MRI	CT
Spine	CT or MRI	Radiographs (myelogram)
Thorax	CT	Radiographs, ultrasound
Abdomen	Ultrasound	CT, radiographs
Pelvis	CT	MRI, radiographs
Muscle	MRI	CT, ultrasound

Ultrasound

Ultrasound allows more accurate evaluation of abdominal tumours than plain radiographs, allowing location and regional spread to be determined. The infiltrative nature of MCT and lymphosarcoma means that ultrasound is the modality of choice for looking at visceral metastases. Thoracic ultrasound allows evaluation of the mediastinum, pericardial sac and heart, but is of less value in evaluation of the lungs, except of course when there is an obviously large mass. Ultrasound is a good diagnostic tool for the preliminary evaluation of the retrobulbar space, although if CT/MRI are available, these imaging modalities are superior. The limitation of ultrasound is in determining tumour from non-tumour – for example, nodular hyperplasia of the liver from liver metastases, splenic haemangiosarcoma from splenic haematoma (Wrigley 1991). The great benefit of ultrasound is that ultrasound-guided biopsies or FNAs can be taken, allowing for non-surgical diagnosis of intra-abdominal and some intrathoracic neoplasias.

CT/MRI

The gold standard for evaluation of pulmonary metastases is CT (see **Figure 3.4**). It also allows better evaluation of bony

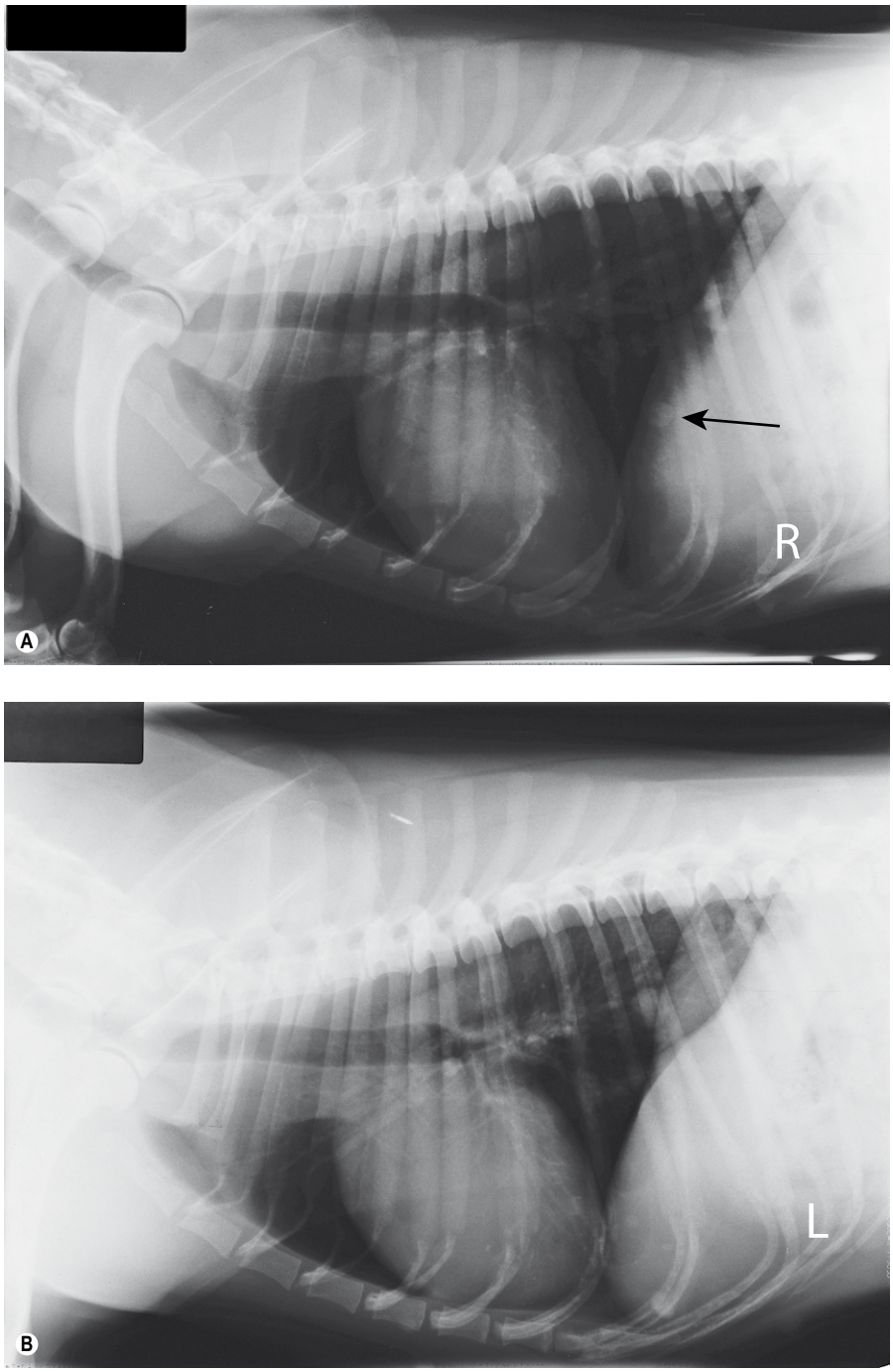


Figure 3.3 Radiographs of early metastatic disease showing the importance of (**A**) right and (**B**) left laterals.

lesions, including the extent of bone tumours and the involvement of bone in soft tissue tumours adjacent to bone. Presurgical planning is facilitated by three-dimensional (3-D) reconstructions and CT scans can be integrated with radiotherapy planning systems for the accurate delivery of radiation (see Chapter 7). CT is also valuable in imaging brain and spinal cord, although in many cases MRI is preferable for brain. CT is a versatile diagnostic with 3-D reconstructions, CT-guided biopsies and integration with radiotherapy planning systems.

MRI allows better evaluation of soft tissues and brain than CT, but as both CT and MRI are expensive to install and maintain, often the availability of either or both modalities is limited.

Rhinoscopy/endoscopy/colonoscopy

Rhinoscopy is valuable in the work-up of the patient with a suspected nasal tumour, preferably in conjunction with CT/nasal radiographs. The major problem with rhinoscopy is obtaining a diagnostic biopsy and the authors prefer to localize the tumour via CT, and, after visualizing the tumour, obtain 'blind-grab' biopsies to ensure getting a large enough

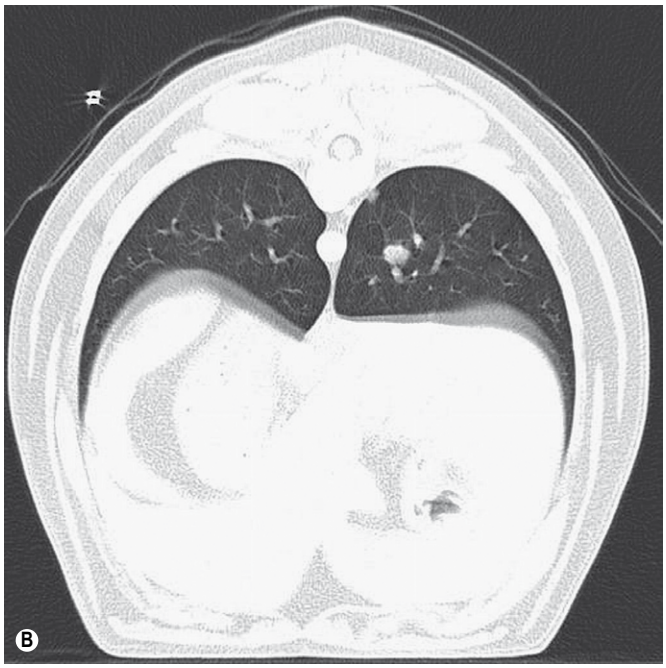
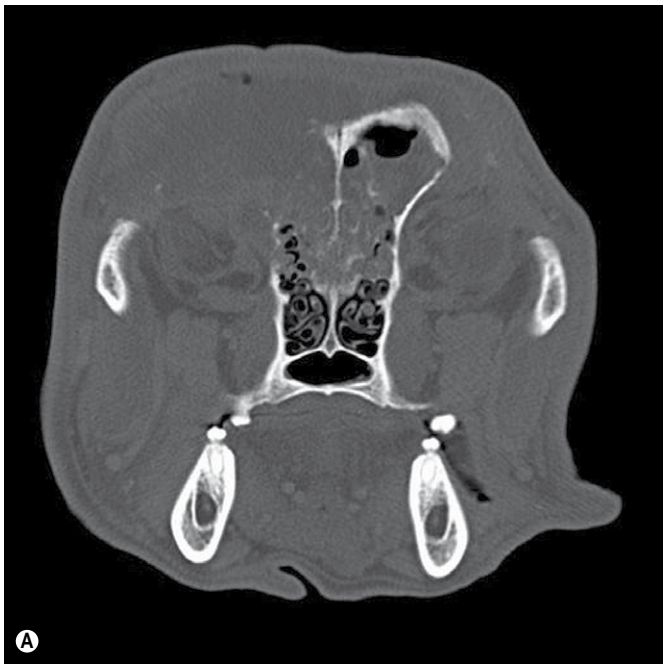


Figure 3.4 (**A**) A modern CT scanner. (**B**) Early pulmonary metastases identified on CT.



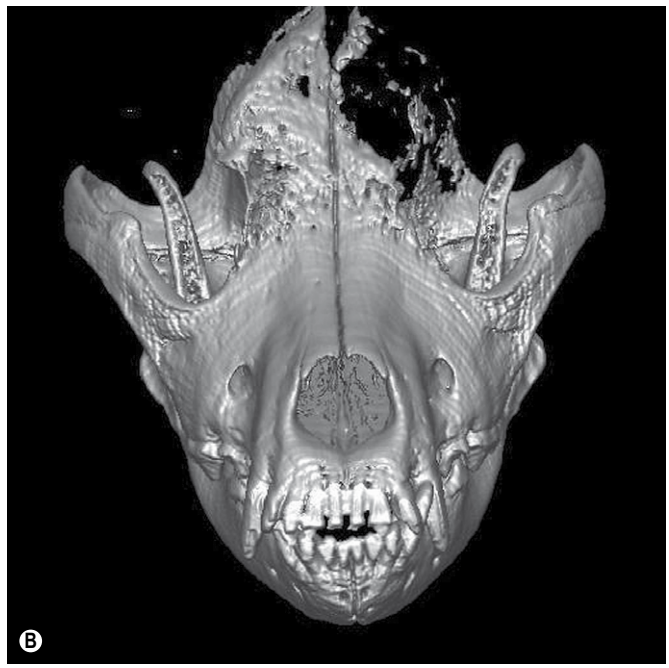


Figure 3.5 (**A**) CT scan of a dog with extensive tumour of the frontal sinus. (**B**) 3-D reconstruction.

piece of tumour tissue to be diagnostic. Scoping can sometimes be used immediately before and after a blind biopsy to visualize if the tumour was biopsied. 'Blind-grab' transnasal biopsies can be performed using alligator rongeurs or a large-bore plastic cannula (Withrow et al 1985). Upper and lower gastrointestinal endoscopies are valuable for examining the stomach, duodenum and colon. The advantage is that it is non-invasive; the disadvantage is that the samples are small and may be non-representative, with definitive surgery still being necessary.

Staging/grading

The purpose of a full diagnostic work-up is to obtain as much information as possible about the patient and the cancer. With this information the treatment plan can be tailored in a manner that gives the patient the best chance of a good quality/quantity of life and makes the client comfortable with their decision as to treatment. On a practical note, the clinician should be aware of treatment costs as well as diagnostic costs and discuss with the client alternative options if finance is a limiting factor. There is no value to the patient in having every diagnostic test possible if the client can then no longer afford treatment!

With a complete work-up the patient is now staged. Staging is based on TNM (tumour, node, metastasis) and attempts to quantify the extent of tumour growth and spread with prognosis. The actual TNM breakdown depends on the individual tumour and will be addressed in the relevant chapters (Owen 1980). It is important therefore to understand the location of regional lymph nodes and their drainage patterns (**Figure 3.6**).

In many cases the grade is also highly prognostic and is determined by the pathologist on examination of the tissue sample. Criteria have been established for most canine and feline tumours and include the mitotic index, degree of anaplasia, degree of invasion, presence of metastatic foci within vessels, etc.

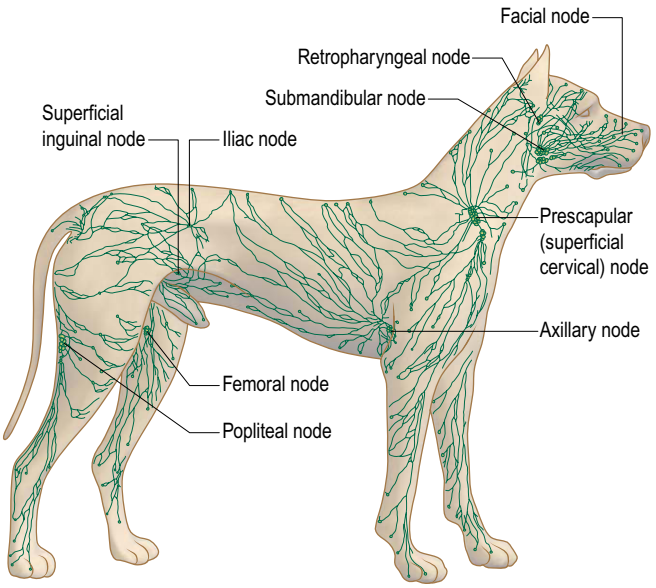


Figure 3.6 Location of the major lymph nodes in the dog and their drainage pattern.

Once the veterinary surgeon has the relevant information regarding the cancer patient the appropriate treatment options for the individual should be discussed with the client.

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Withrow SJ, Susaneck SJ, Macy DW et al 1985 Aspiration and punch biopsy techniques for nasal tumours. Journal of the American Animal Hospital Association 21:551–554

Wrigley RH 1991 Ultrasonography of the spleen. Life-threatening splenic disorders. Problems in Veterinary Medicine 3:574–581

Principles of cytology and pathology

Cytology

Cytology is a quick, usually simple and inexpensive method of screening 'lumps and bumps'. It is indicated for most palpable external masses and is useful for some internal masses or generalized diffuse organ changes with the assistance of ultrasound. It is also a valuable tool for examining effusions in body cavities, 'washes' (e.g. bronchoalveolar lavages (BAL), prostatic washes) and cerebrospinal fluid (CSF) analysis. Although cytology is useful in differentiating between tumour and non-tumour (e.g. infectious/inflammatory processes), when examining slides for suspected neoplasia it is important to remember that certain tumour cells generally exfoliate better than others, i.e. round cells > epithelial > mesenchymal. Impression smears taken from biopsy samples are also useful intra-operatively, especially if the type of lesion may affect the procedure and the ability to examine frozen sections is not available.

Slide preparation

The collection of cells and preparation of the slide are important as cells can be damaged and distorted when making preparations, making interpretation difficult or impossible (Villiers & Dunn 1998). Two techniques for obtaining samples from solid masses are used. In the first technique a needle is attached to a syringe (usually 5 or 10 ml), the needle is placed in the structure to be analysed and suction applied by drawing air into the syringe with the needle in the tissue. The aspirated tissue is expelled onto a clean slide, smeared using a second slide and stained. The second technique is known as fine-needle capillary sampling and involves simply placing the needle with no syringe into the tissue, usually two or three times; cells are displaced into the cylinder of the needle and are then expelled onto a slide as before. The latter technique may reduce the possibility of blood contamination and reduce damage to fragile cells.

Staining the slide

Most veterinary practices routinely use Romanowsky-type stains for staining in-house slide preparations. It is important to remember that the length of time for 'dipping' depends on the age of the stain (the stains should be changed regularly to ensure good results) and the cellularity of the preparation. Stains should be protected from light, kept covered when not in use and should be filtered periodically to eliminate debris and possible contaminants.

Examining the specimen

Once the specimen has been prepared, stained and dried, it should be examined systematically (**Figure 4.1**). Scan the whole slide under low power and then focus in on areas of interest. Remember that more than one process may be occurring at one time – for example, a tumour may have a secondary inflammatory or infectious component associated with it.

The initial step is to decide whether or not the lesion is inflammatory or non-inflammatory. Tumours are seen more frequently in middle-aged to older animals, whereas inflammatory lesions can occur at all life stages. Investment in a good cytology text is important for gaining experience in identifying neoplastic and non-neoplastic cytology (Baker & Lumsden 2000).

The major characteristic of active inflammation is the presence of the segmented neutrophil (**Figure 4.2A**). This can occur either as a consequence of infectious or non-infectious causes. Progression of inflammation to the chronic phase is characterized by the presence of macrophages in addition to neutrophils (**Figure 4.2B,C**). In certain cases it can be difficult to differentiate between macrophages (histiocytes) and neoplastic cells; if there is any doubt, a fresh unstained sample should be submitted for review by a clinical pathologist.

Remember inflammation/infection can be a component of neoplasms so for ulcerated cutaneous lesions a biopsy is recommended. The clinical history should always be considered in conjunction with the specimen.

Once inflammatory lesions have been ruled out, non-inflammatory causes should be considered.

Cytological preparations that would be non-neoplastic include 'cystic' structures, normal structures (e.g. fat, salivary glands) (**Figure 4.2D**) and hyperplastic tissue (reactive fibroblasts in recent scar tissue).

Neoplastic tissue, by definition, means 'new growth' so the criteria for defining potential neoplasia on cytology are cell type and the characteristics of malignancy. Caution must be applied when using the latter criterion on cytological specimens as hyperplasia (reactive features) and neoplasia can appear cytologically very similar – for example, it can be very difficult to differentiate between reactive mesothelial cells and neoplastic epithelial cells. If you are sure that the sample you are examining is from a tumour, the next question to resolve is whether or not it is benign or malignant. Common benign tumours include histiocytoma and perianal adenoma (**Figure 4.3**).

The criteria of malignancy to look for when examining a cytological preparation are outlined in Box 4.1.

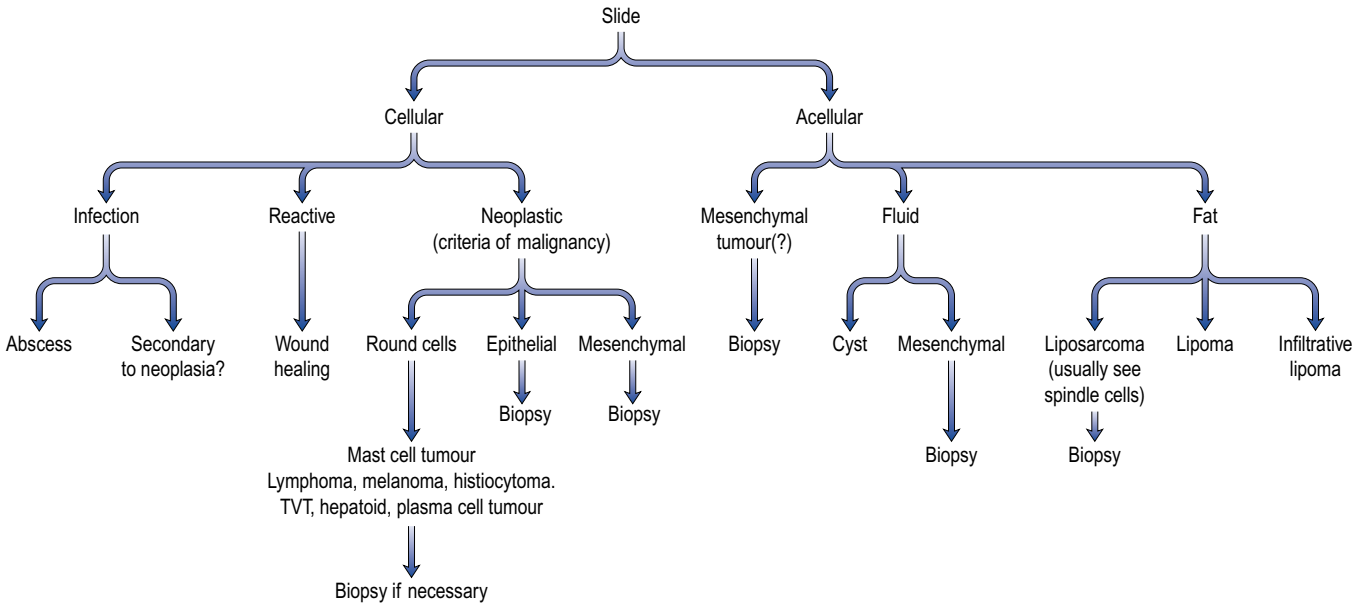


Figure 4.1 Flow chart showing approach to evaluating FNAs.

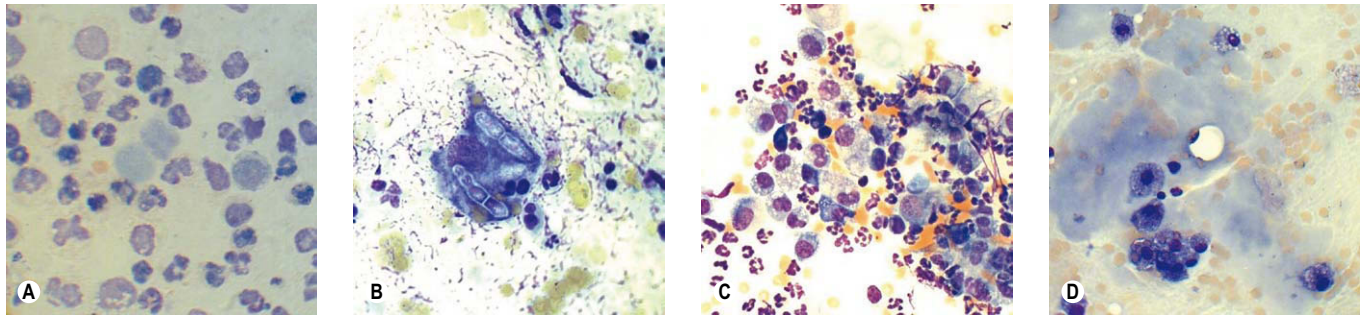


Figure 4.2 Non-neoplastic conditions (original magnification 500). (**A**) Suppurative inflammation/abscess; (**B**) pyogranulomatous inflammation secondary to fungal infection; (**C**) pyogranulomatous effusion; (**D**) salivary mucocele. (Courtesy K. Freeman.)

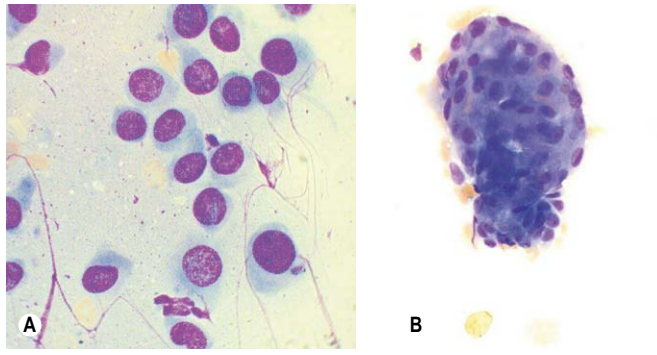


Figure 4.3 Benign cutaneous tumours (original magnification 500). (**A**) Canine histiocytoma; (**B**) perianal adenoma. (Courtesy K. Freeman.)

What is the next step?

If you are sure your sample is representative and you have ruled out the above non-neoplastic options, then it is important to characterize the type of tumour.

Tumours are classified into four broad categories:

- 'round cell' tumours
- epithelial cell tumours
- mesenchymal cell tumours
- neuroendocrine tumours.

Box 4.1

Criteria of malignancy in a cytological preparation

- Asymmetric mitotic figures
- Multinucleation
- Abnormal chromatin clumping/distribution
- Anisocytosis (variable cell size)
- Pleomorphism (variable shape)
- Anisokaryosis (variable nuclear cell size)
- Variable nucleolar size, shape or multiple nucleoli
- Changes in nuclear to cytoplasmic ratio

'Round cell' tumours

These cells exfoliate very well and are characterized by being 'round' in appearance and appearing on a slide as single cells. Common round cell tumours that can be identified on cytology include lymphoma, plasma cell tumour, histiocytoma, mast cell tumour, melanoma, transmissible venereal tumour (TVT), hepatoid tumour (also may appear epithelial) and anaplastic tumours of any type (**Figure 4.4**).

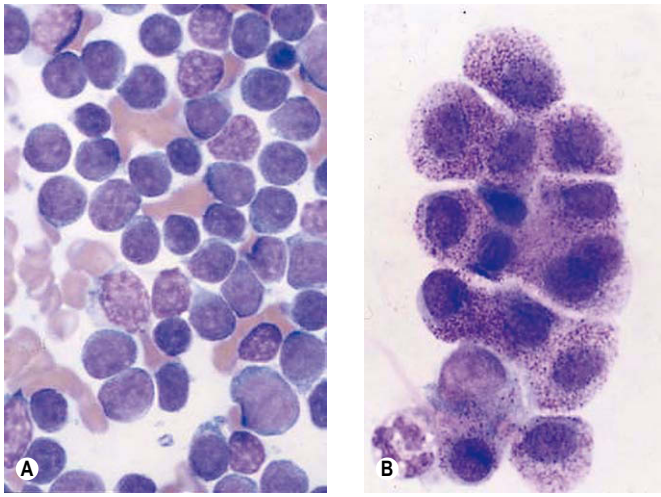


Figure 4.4 Round cell tumours. (**A**) Lymphoma; (**B**) mast cell tumour.

Epithelial cell tumours

Epithelial cells exfoliate well and are typified by forming 'rafts' of cells with definite borders between cells because of the presence of tight junctions giving the appearance of a cobblestone pattern. Sometimes glandular and papillary configurations can be recognized.

Mesenchymal cell tumours

Cells of mesenchymal origin do not, as a rule, exfoliate well. Often a low yield of cells on an aspirate can be suggestive of mesenchymal origin (e.g. a sarcoma). On cytology these cells often have indistinct cell borders so it is difficult to delineate the end of the cytoplasmic border of one cell and the beginning of the next cell. The individual cells are elongated with central or eccentric nuclei (**Figure 4.5**).

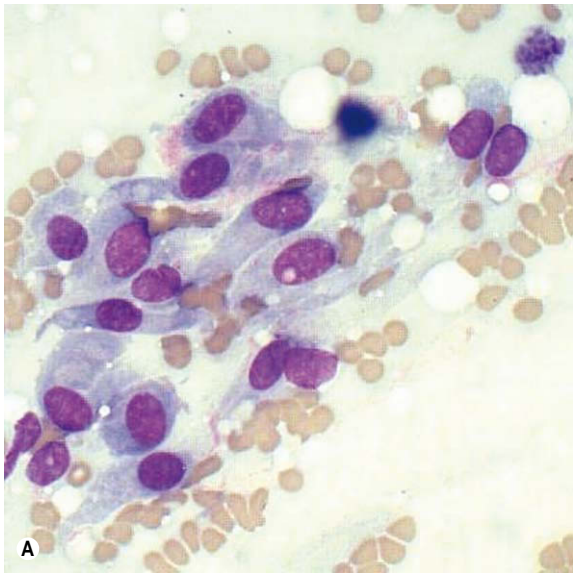
It is important to remember that cytology is an important diagnostic tool but can on occasions be misleading, as sometimes it is not possible to differentiate cell type. A biopsy is usually the more accurate diagnostic tool in such circumstances.

Neuroendocrine tumours

These relatively rare tumours are characterized by possessing round to oval nuclei, often located within a 'sea' of cytoplasm. Some discrete cells may have granular or finely vacuolated cytoplasm and features of malignancy may be very subtle.

Cytological evaluation of lymph nodes

Evaluation of regional lymph nodes is an essential part of staging and, depending on the tumour type (mast cell tumours, epithelial tumours, melanomas), the lymph nodes can be the first site of dissemination. Sarcomas more typically spread haematogenously, but aggressive sarcomas can also involve the regional lymph nodes. Although fine needle aspirates (FNAs) are the backbone of staging from regional lymph nodes, it is important to remember that in equivocal cases excisional biopsies are required; palpation alone is inadequate to assess the possibility of metastatic spread (Langenbach et al 2001). Whenever possible the sentinel node should be removed at the time of surgery, irrespective of the results of cytology.



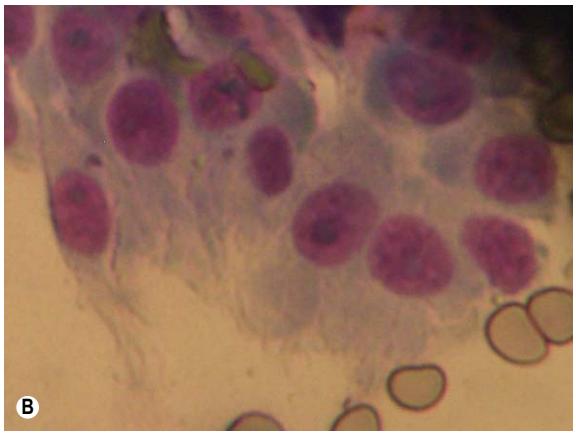


Figure 4.5 Mesenchymal cell cytology (original magnification 500). (**A**) Soft tissue sarcoma; (**B**) Osteosarcoma. (Courtesy K. Freeman.)

Cytological evaluation from body cavities: effusions

In any patient with an effusion evaluation of the fluid can provide a great deal of information concerning the underlying disease process. Typically effusions are classified as transudate, modified transudate and exudate (Table 4.1):

- transudates are usually due to hypoalbuminaemia or early cardiac insufficiency and are typically non-inflammatory
- modified transudates arise from a variety of causes
- exudates are usually infectious, inflammatory or neoplastic.

Chylous effusions

Chylous effusions can result from neoplastic and non-neoplastic conditions and are a consequence of leakage from the thoracic duct or other lymphatics. They are characterized by sudanophilic droplets (chylomicra) with triglyceride levels greater than in serum, the latter being the most diagnostic test (Hawkins & Fossum 2000). The fluid clears on alkalinization and ether extraction; the predominant cell population is small

lymphocytes. Differentials include feline cardiac disease, thoracic duct rupture and lymphatic obstruction (neoplastic or non-neoplastic).

Pseudochylous effusions

A pseudochylous effusion must be differentiated from a true chylous effusion and is characterized by the absence of Sudan staining, failure to clear with ether (although some clear with alkalinization) and triglyceride levels lower than in serum; small lymphocytes are the predominant population. Differentials include feline cardiac disease.

Haemorrhagic effusions

Haemorrhagic effusions are characterized by the packed cell volume (PCV) of the effusion being close to that of the peripheral blood PCV. An effusion may look bloody but the PCV of the fluid must always be checked against the circulatory PCV. Differentials for haemorrhagic effusions include trauma, neoplasia (primary/secondary bleeding tumour, DIC) and anticoagulants (e.g. rodenticide).

Malignant effusions

The presence of a malignant effusion warrants a guarded prognosis (**Figure 4.6**). Tumours that may result in a malignant effusion include lymphomas, carcinomas (carcinomatosis) and mesothelioma. Carcinoma cells may leak from lymphatics and implant onto serosal surfaces and eventually undergo desquamation into fluid; this is most frequently seen with mammary carcinomas, especially feline, prostatic and pancreatic carcinomas. Sarcomas rarely produce an effusion containing neoplastic cells.

For patients with suspected effusions, thoracic and/or abdominal radiographs are required and a sample of fluid withdrawn, often under sedation, if necessary. For patients with only a small amount of fluid, ultrasound guidance may be necessary.

Table 4.1 The characteristics of effusions

	Transudate	Modified transudate	Exudate
Specific gravity	<1.017	1.017–1.025	>1.025
Total protein (g/dl)	<2.5	2.5–5.0	>3.0
Nucleated cells (per mm^3)	<1000	500–10 000	>5000
Cell types	Mesothelial, monocytes	Lymphocytes, monocytes, red blood cells, mesothelial cells	Neutrophils, red blood cells, monocytes
Examples of underlying causes	Right-sided heart failure in cats	Heart failure, diaphragmatic hernia, neoplasia	Sepsis, lung-lobe torsion, neoplasia

Pericardial effusions

Pericardial effusions can be seen in conjunction with malignant heart tumours, typically auricular haemangiosarcomas. The ability to differentiate between neoplastic and non-neoplastic causes would be beneficial from both a diagnostic and prognostic point of view. A number of studies have looked at cytology, pH and other biochemical variables, but all studies had significant overlap between the two groups (Laforcade et al 2005) or contradictory values were obtained (Edwards 1996, Fine et al 2003), meaning that although cytological evaluation of the fluid is helpful, ultimately it is the visualization of tumour that distinguishes neoplastic effusion from idiopathic.

Cytological evaluation of visceral structures

Cytological evaluation of abnormalities detected on ultrasound and using ultrasound guidance is of great value as this can often reduce the necessity for invasive surgery, or allow presurgical planning.

The diagnosis of lymphoma involving internal organs can be made solely on FNAs of the liver, spleen, kidney, etc.

Hepatic and splenic nodules can be aspirated but care must be used in interpretation, as hyperplastic nodules are common in older animals.

Staging of tumours such as mast cell tumours can be achieved using ultrasound-guided FNAs of abnormal liver/spleen or lymph nodes (**Figure 4.7**). However, caution must be used in interpretation of these aspirates as mast cells are normally seen in small numbers in these organs (see Chapter 19 for more discussion on staging mast cell tumours). For patients with cutaneous mast cell tumours, if the liver and

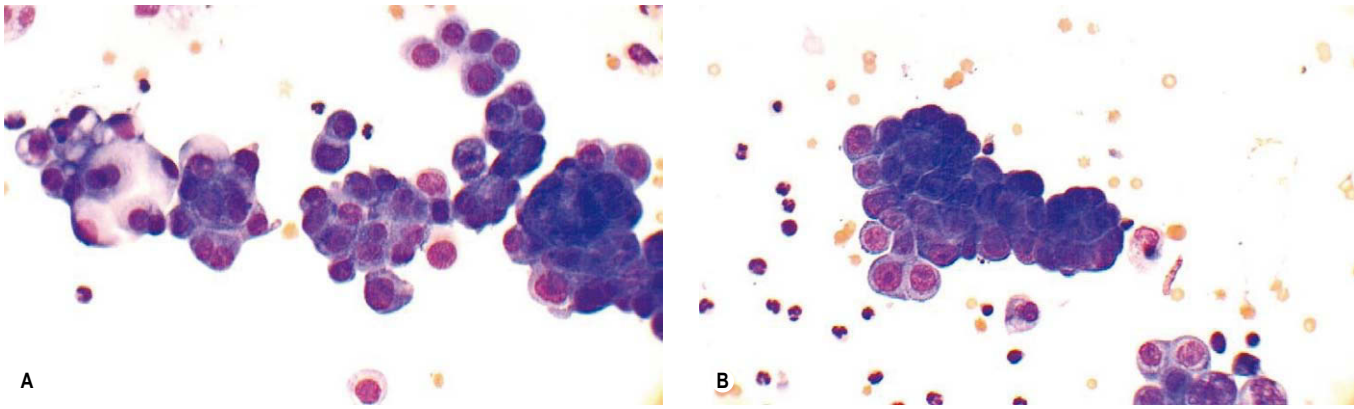


Figure 4.6 Malignant effusions (original magnification 500). (**A**) Malignant effusion (cat); (**B**) malignant pleural effusion. (Courtesy K. Freeman.)

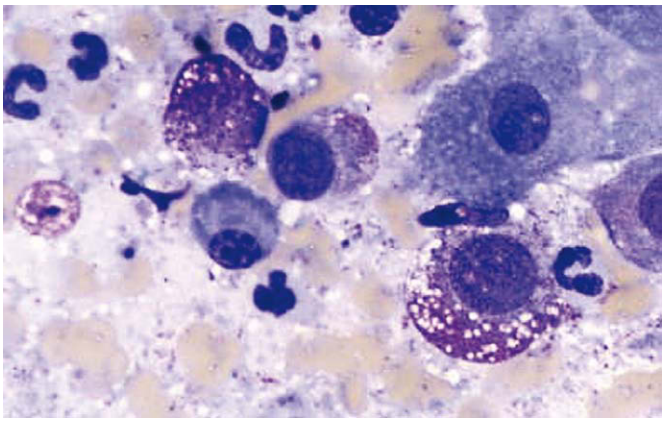


Figure 4.7 Metastatic mast cell tumour to liver.

spleen appear normal on ultrasound then FNAs are not necessary (Finora et al 2006). FNAs of enlarged lymph nodes can help to differentiate neoplastic from reactive nodes.

In the thorax, the most common application of ultrasound-guided FNAs is for mediastinal masses to distinguish between lymphoma and thymoma (Chapter 14). Additionally, metastatic disease to the mediastinal lymph nodes can be examined in some cases. The value of FNAs in the diagnosis of lung tumours is questionable and may lead to seeding of the thorax or iatrogenic pneumothorax, and the authors rarely advise FNAs for lung masses. Bronchoalveolar lavage may be useful for diagnosis of primary pulmonary neoplasia but is not rewarding for metastatic tumours unless they break through the interstitium into the airways.

Histopathology

In cases where cytology is non-diagnostic or inappropriate, it is important to obtain a tissue biopsy. The importance of obtaining a biopsy before proceeding to definitive surgery is extremely important and cannot be overemphasized. However, the quality of the information given by the pathologist depends on the quality of the submitted specimen. A discussion on biopsy techniques can be found in Chapter 5. In addition to the diagnosis, biopsy material also allows the malignant potential of the tumour to be characterized based on the degree of differentiation, invasion, necrosis, destruction of surrounding normal tissue and the presence of micrometastases within small blood vessels and lymphatics. Grading schemes have been adopted for a variety of tumour types and these will be discussed in the appropriate chapters. Tumour grade can be highly prognostic and can help guide treatment planning.

Submission of tissue samples

Tissue should be placed in neutral buffered formalin at a volume of 1 part tissue to 10 parts formalin (10%) to allow for adequate fixation. Tissue pieces greater than 1–2 cm may require incisions to be made into the tissue to allow penetration of the fixative: this can be done in a 'bread loaf' pattern allowing multiple cuts into one surface but leaving the other surface intact to preserve orientation.

The margins should not be compromised by the fixation because, in many cases, this is an essential part of the report and may influence the oncologists' decision whether or not to recommend further treatment. Ensure that the orientation of the specimen provided is clear to the pathologist. If you are particularly concerned about a specific margin, mark it and let the pathologist know. Margins can be marked with suture material or India ink.

Wherever possible submit the entire specimen. With large specimens fix the tissue well first, for at least 48 hours, then wrap it in formalin-soaked 4 4 sponges before submission to the laboratory. If the specimen is too large, submit representative samples from the tissue but keep the whole specimen until you are confident with the report. Large splenic tumours are a particular example of this circumstance. Remember, haematomas, haemangiomas and haemangiosarcomas can look the same macroscopically and the diagnosis of a splenic haematoma on a single piece of tissue only would merit a re-submission to be absolutely sure of the diagnosis.

Communication with the pathologist is essential. Complete the section on signalment and clinical history, especially previous treatment/surgery, as this information is important to the pathologist. When margin evaluation is required a small diagram can be extremely helpful. Do not be afraid to call up your pathologist to discuss the results; they, like everyone else, are very busy but will always find time to go over results with you. It is important to interpret histopathology reports logically in the context of what you are seeing in the individual patient – remember, 'Common things occur commonly, uncommon things uncommonly'. In some instances more tissue or a larger sample may be necessary to arrive at a diagnosis.

Special stains

In the majority of cases the histopathology report is based on the light microscopic examination of haematoxylin and eosin stained slides that have been fixed in formalin and then paraffin embedded. However, it is not always possible for the pathologist to fully characterize the tumour using this method alone and a report describing the specimen as poorly differentiated or anaplastic may be sent. In such circumstances the use of additional stains is recommended to delineate the origins of the neoplastic cells.

The value of immunohistochemistry in veterinary oncology is finally being appreciated. The application of these stains (Table 4.2) to all samples seen as poorly differentiated enables the oncologist to have a better understanding of the potential biological behaviour of the tumour and the best treatment options for the patient. Typically 'anaplastic' tumours that have lost their original morphological characteristics would be expected to behave aggressively in the patient with early metastatic spread, irrespective of tissue of origin. The most common application of immunohistochemistry is in lymphomas to differentiate between T and B cells, as this is of prognostic significance. With the apparent increase in the diagnosis of histiocytic disease, it is advisable for any tumour that might possibly be histiocytic in origin to have definitive immunohistochemistry performed.

Flow cytometry (Table 4.3) makes it possible to distinguish myeloid from lymphoid leukaemias and to classify lymphoid leukaemias and lymphomas accurately by immunophenotype

Table 4.2 Immunohistochemistry on solid tumours

Immunohistochemical stain	Cell type	Comments
Cytokeratin	Epithelial	Distinguishes carcinomas from sarcomas
Vimentin	Mesenchymal	Distinguishes sarcomas from carcinomas
S-100	Melanocytes and cells of nervous origin	Not specific for malignant melanomas and in some cases chondrosarcomas can be positive as can ductal epithelial cells
Melanin-A	Melanocytes	Does not always stain poorly pigmented tumours
Factor VIII/vWF	Endothelial cells	Distinguishes haemangiosarcomas from other sarcomas
Desmin	Muscle cells	
Actin	Muscle cells	
Chromogranin A	Neuroendocrine	
Neuron-specific enolase (NSE)	Nervous system	
Glial fibrillary acidic protein (GFAP)	Glial cells	Glial tumours
CD18	Common leucocyte antigen	Lymphoma, mast cell tumours, histiocytic sarcomas, granulocytes
Toluidine blue	Mast cells	Mast cell tumours
CD3	T lymphocyte	T-cell lymphomas
CD79a	B lymphocyte	B-cell lymphomas
CD45	Common leucocyte antigen	Lymphomas
Synaptophysin	Neuroendocrine	Neuroendocrine tumours
Tryptase	Mast cells	Mast cell tumour
Fascin	Dendritic cells, histiocytic cells	Histiocytic disease

Table 4.3 Flow cytometry for lymphomas and leukaemias

Antibody	Cells identified
CD3, CD3-e	T cells
CD4	T cells (helper)
CD8	T cells (cytotoxic)
CD5	T cells and subset B cells
CD79a	B cells
CD45	B cells
CD21	B cells
CD11a	Leucocytes, histiocytes
CD11b	Granulocytes, monocytes, histiocytes
CD11d	Large granular lymphocytes
CD14	Monocytes
CD34	Stem cells, primitive leukaemic blast cells
CD45	Leucocytes
CD41	Megakaryoblasts and platelets
MPO	Granulocytes
MAC387	Neutrophils and monocytes/macrophages
CAD048	Neutrophils (neutrophil specific antibody)

(Vernau & Moore 1999, Villiers et al 2006). Because the accurate differentiation of leukaemias helps determine the prognosis and treatment plan, flow cytometry should be seen as the gold standard for these cases. Flow cytometry is also a useful diagnostic tool to differentiate between the two major tumours of the mediastinum – thymoma and lymphoma – and is indicated in cases where routine cytology was not definitive (Lana et al 2006).

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Concepts of oncology surgery

What role does surgery play in the treatment of cancer? This is variable, but virtually all cancer patients have some sort of surgical event, whether it is a biopsy to obtain the diagnosis or definitive surgical treatment. Some types of cancer can be cured with surgery; other times, palliation is the goal. A surgical oncologist must be adaptable. Sometimes a delicate, minimally disruptive surgery is prudent; at other times, more aggressive or extensive surgery would best suit the patient. It is important to administer the correct surgical dose (intralesional, marginal, wide or radical) to best fit the particular cancer patient and the availability and suitability of adjuvant treatments such as radiation therapy. The ability to modify surgical technique and surgical expectations to suit the individual case is a unique and valuable skill. Consider how differently the cancer surgeon must approach solid tumours of the skin and subcutaneous tissues, bowel obstruction due to mesenteric lymph node enlargement, intranasal tumours, solid tumours of the anal sac and lymphoma.

The goal of this chapter is to explain the concepts of surgical oncology; however, 'cancer does what cancer wants', and broad generalizations are difficult. A thinking surgeon is required, preferably working in conjunction with a medical oncologist, a radiation oncologist, a radiologist, a pathologist and so on, so that the animal as a whole is considered, not just its tumour (see Chapter 3). The following sections in this chapter deal with important points to convey the concepts of surgical oncology.

What am I treating?

Let us start with a diagnosis. It is important to point out that diagnostic imaging and physical examination can provide valuable information, but are never going to give a definitive diagnosis of the exact tumour type. Extracting cells from the patient (cytology or histopathology) to ascertain the type of cancer being treated prior to the actual definitive treatment is very important. Further work-up, treatment type (e.g. chemotherapy, radiation therapy, marginal versus wide surgical resection) and prognosis can change markedly with an accurate diagnosis. For example, a subcutaneous lipoma can look and feel exactly the same as a mast cell tumour. By way of another example, assumptions that liver masses seen on ultrasound are neoplastic or benign cannot be accurate; you cannot be sure until you have some tissue or cells for examination. Guesswork is, by definition, uncertain and should not be used to condemn a patient to a poor prognosis, or to wrongly assume a good prognosis. Remember, a lump is a lump until it has been sampled!

However, in certain cases a preoperative biopsy is an unnecessary or risky step and is not indicated.

When to biopsy?

When the result of the biopsy would change the way you would treat (e.g. chemotherapy if the mediastinal mass is a lymphoma or surgery if it is thymoma), then a biopsy is indicated. Conversely, if treatment would not change – for example, lung lobectomy for a solitary lung mass (granuloma or primary lung tumour) or splenectomy for a localized bleeding splenic mass (benign or malignant), or if the biopsy is as difficult or dangerous as the curative treatment (e.g. spinal cord biopsy), then the biopsy information should be obtained after surgical removal (Ehrhart & Withrow 2007).

Another consideration for acquiring a preoperative biopsy is in the situation where the client's willingness to treat would depend on the tumour type and the attending prognosis (Ehrhart & Withrow 2007). For instance, a client may be willing to perform a mandibulectomy for oral squamous cell carcinoma (SCC) but not for amelanotic melanoma. A large melanoma carries a far worse prognosis than a rostrally located SCC and both can look the same grossly. Only a biopsy can differentiate them accurately, so in this case a preoperative biopsy is indicated.

What am I treating?

Cytology: fine needle aspirate (FNA) cytology

This is a great place to start on the hunt for a diagnosis. Cytology is not equivalent to histopathology, so it is not a 'biopsy', but a very good first line at gaining cellular material for a diagnosis. For externally accessible masses this is an easy, cost-effective, low-risk technique and very important information is often obtained (see Chapter 6). Ensure all skin or subcutaneous lumps undergo FNA!

Biopsy methods

The three tenets of oncology are Biopsy! Biopsy! Biopsy! This is the most important point of this chapter. There are a number of biopsy techniques to consider and the selection depends on the particular clinical setting and operator skill and preference (Table 5.1).

Table 5.1 Some examples of indications for incisional versus excisional biopsy

Tumour type	Biopsy type
Intranasal	Incisional (usually)
Solitary liver mass	Excisional, with wide margin if possible
Diffuse liver masses	Incisional
Solitary lung mass	Excisional, with wide margin if possible
Solitary gastrointestinal	Excisional, with wide (5–6 cm) margin if possible
Multiple gastrointestinal	Incisional
Localized splenic mass(es)	Excisional

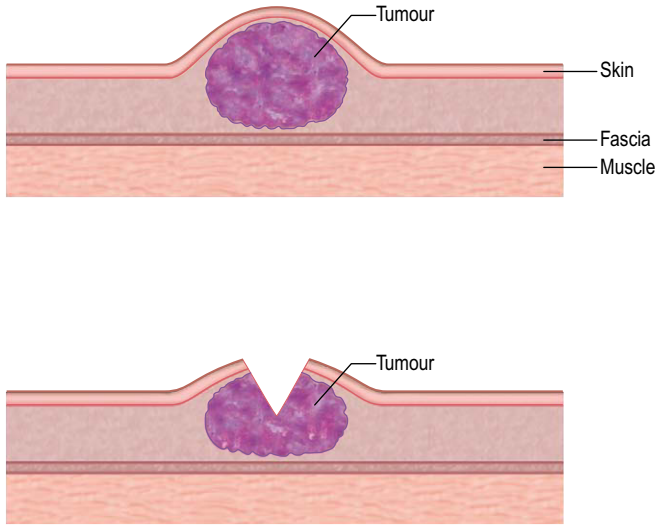


Figure 5.1 Incisional (wedge) biopsy.

Incisional biopsy

Needle core/'tru-cut' biopsy

This is a minimally invasive method of obtaining tissue, and is an example of an incisional biopsy. It can be done under sedation on an outpatient basis. Usually three samples are taken. The problem is that only small tissue samples are obtained, and if there is friable, very vascular or necrotic tissue, this can hinder the pathologist's diagnosis (e.g. haemangiosarcomas, oral masses). If only small bits of tissue are obtained, it may be better to try an incisional (wedge) biopsy. Tru-cut biopsies can be used for external or internal lesions (e.g. ultrasound-guided liver, spleen, kidney, prostate, mediastinal mass, etc.). A Jam-shidi bone biopsy punch is a similar concept used to biopsy bony lesions (but must be done under general anaesthesia). It is important to use any punch or needle device correctly and accurately to ensure you deliver to the pathologist a representative tissue sample for histopathology.

Punch biopsy

This is a short and wide biopsy (as opposed to the long thin sample retrieved by needle devices) and can be used on any external tumour (oral, perianal, skin). A short general anaesthetic is usually required. Some also use this technique for liver biopsy at the time of open surgery.

Wedge biopsy (Figure 5.1)

This also typically involves a general anaesthetic and a minor surgery. For large, ulcerated, external masses where innervated host tissue does not need to be penetrated (tumours do not have nociceptors), a biopsy may be obtained without sedation or anaesthesia. Generally, the skin is cleaned and prepared aseptically and a scalpel blade is used to incise the skin and underlying tumour to remove a wedge of tissue. Incisional biopsy is employed if the surgeon has any doubt about compromising the definitive surgery with a larger (excisional) biopsy (Figures 5.2 and 5.3).

It is very important not to compromise curative resection. Remember that the incisional biopsy tract must be removed en bloc with the rest of the tumour at subsequent resection. Small incisions are better than large ones that contaminate uninvolved tissue planes with implanted cancer cells and make further surgery more difficult.

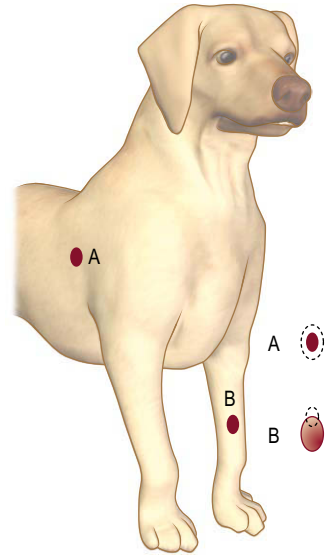


Figure 5.2 Biopsy technique and location. A. The location of this mass is in an area where there is more loose skin. If a tumour of this size was removed via a marginal resection (excisional biopsy), a second surgery to achieve wider margins (if necessary) is still possible. B. The location of this mass is in an area where there is minimal loose skin or deep layers of fascia. Therefore incomplete resection of a malignant mass will compromise a further definitive surgery. The tumour type in this location should be known before removal. An incisional biopsy should be performed first, remembering that the biopsy tract will be removed en bloc with the tumour at a subsequent aggressive resection or included in the irradiated field.

The absolute aim of the procedure is a diagnosis without compromising the prognosis. Although the patient may have to undergo another surgical procedure, the information obtained from this step can be invaluable (see above, 'When to biopsy?'). Bleeding must be controlled and infection avoided. Haematomas, seromas and abscesses all increase the risk of spreading cancer cells locally. Drains must not be used in incisional or close excisional biopsies.

When obtaining an incisional biopsy, obtain the sample from the edge, not the middle of the tumour. In the latter case

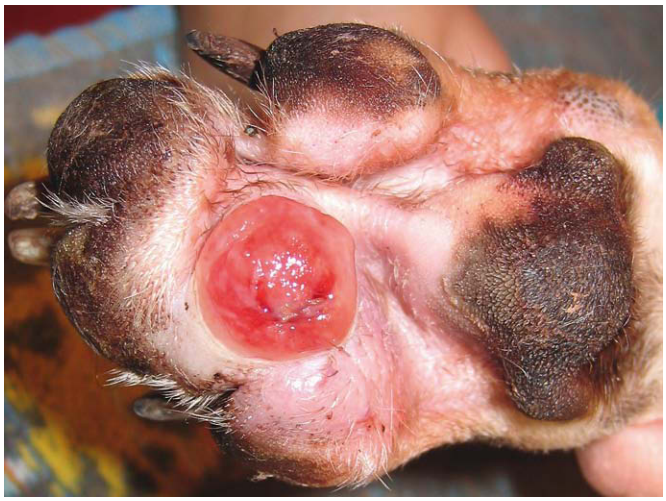


Figure 5.3 Incisional biopsy is appropriate due to location.

a non-healing wound may develop, and if the patient is not a candidate for surgical excision (e.g. a large sarcoma close to the anus), it may lead to problems with palliative therapy (e.g. radiotherapy).

Excisional biopsy

This is performed when knowing the tumour type would not change the treatment (e.g. lung lobectomy for solitary lung mass, 'benign' skin tumours, splenectomy for solitary splenic mass, liver lobectomy for solitary liver mass, orchiectomy for testicular tumour, etc.). In other words, the surgeon is confident the patient will not be compromised in the event that close or incomplete margins result, requiring a second wider resection. When used properly on selected cases, excisional biopsy is diagnostic, therapeutic and cost effective (Ehrhart & Withrow 2007).

Excisional biopsies have the connotation of removal of the mass with a cuff of normal tissue adequate to excise benign or small lesions relative to location. However, for malignant masses, it is important to include a wide margin of normal tissue, i.e. a curative excision (**Figure 5.4**). The decision to include a wide margin of normal tissue depends on the ability to achieve this (location, skill) and the tumour type.

Specialized biopsy techniques

These include endoscopic (often inadequate samples obtained), laparoscopic and thorascopic (specialized equipment required), and image-guided (e.g. CT or ultrasound) techniques. Such techniques can be very useful but facilities and operator skill are important considerations.

Once you have your cytological or histopathological diagnosis or both, you must ask yourself the following questions. Do the results fit the clinical picture? Is the pathologist reporting a behaviourally aggressive, locally destructive oral mass as a fibroma? If the report does not fit the clinical picture, contact the pathologist to discuss the findings; send in radiographs or photographs with your biopsy samples. Ensure you have submitted a representative sample. In some cases the pathologist may suggest special stains or a repeat biopsy.

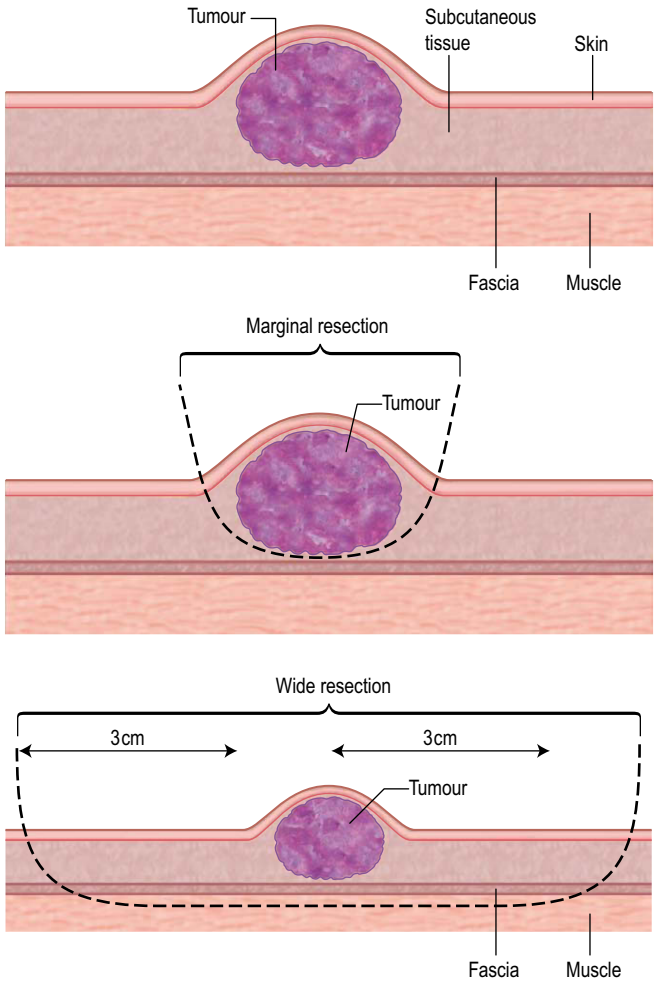


Figure 5.4 Curative surgery versus excisional biopsy.

Planning your surgery

What surgical dose? Is a cure possible?

The first thing to consider is whether or not a surgical cure is possible. Can you cure some cancers with surgery? The answer is absolutely yes. If a surgical cure can be achieved and is in the best interests of the patient, then the surgeon must give the best attempt possible! Cure is almost always embodied in the first surgical procedure, so you have only one good chance.

The biological behaviour of the tumour has a large influence on whether or not it is curable. Consider a dog with a non-metastatic soft tissue sarcoma (STS) of the subcutaneous tissue of the trunk. It is generally accepted that surgical removal of the tumour with wide margins offers the best chance of a cure, provided the tumour has not metastasized.

Consider a second dog with a 5 cm diameter anal sac adenocarcinoma. This tumour has significant metastatic potential, so a surgical cure is unlikely. Removal with 'wide' (3 cm) margins would be very difficult, and would require removal of rectum, causing increased morbidity and complications, and is likely not in the best interests of the patient. A 'smaller' surgery to remove the mass with the widest margin possible with low morbidity, combined with adjuvant chemotherapy, is an accepted protocol which offers a median survival time of 12–36 months (see Chapter 15).

Another factor that has a considerable influence on whether or not a surgical cure is possible is the experience, skill and expertise of the surgeon and the availability of suitable facilities, equipment and staff.

It is sad but all too commonly true that many animals with surgically curable cancers are compromised due to a lack of surgical expertise, resulting in increased morbidity, shorter survival or death. If the surgeon is not capable of the task due to a lack of training or experience, and is not confident of giving the patient the best chance possible, a specialist referral should be sought.

Malignant cancer requires removal with a wide margin of normal tissue. 'Wide' margins usually refer to 2–3 cm margins of grossly normal tissue around the main mass; however, in some cases, 1–2 cm is sufficient (**Figure 5.5**). The first goal is to get the entire tumour out, the second is to close the defect; otherwise, all you have achieved is a large biopsy and compromised a definitive surgery (**Figure 5.6**).

Remember that any drains or tension-relieving holes performed at the time of a 'dirty' excision have to be removed along with the suture line the second time around.

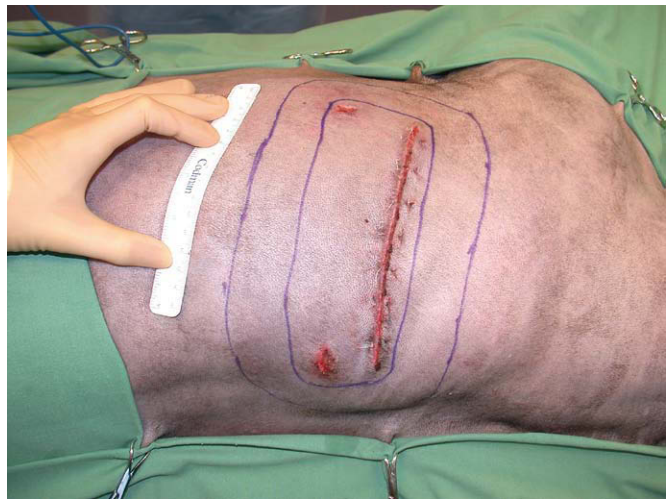
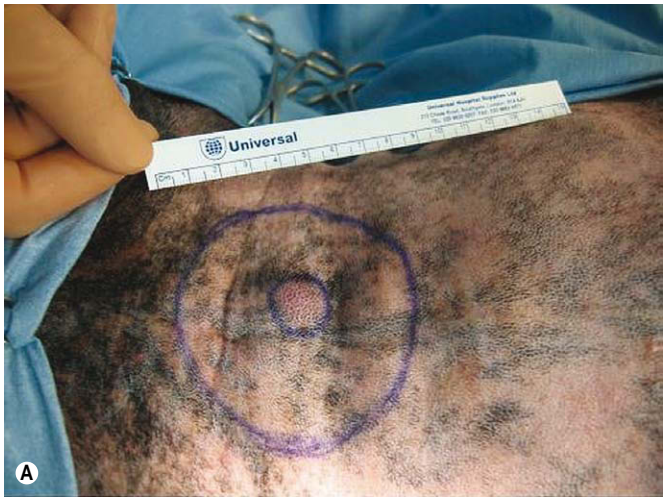
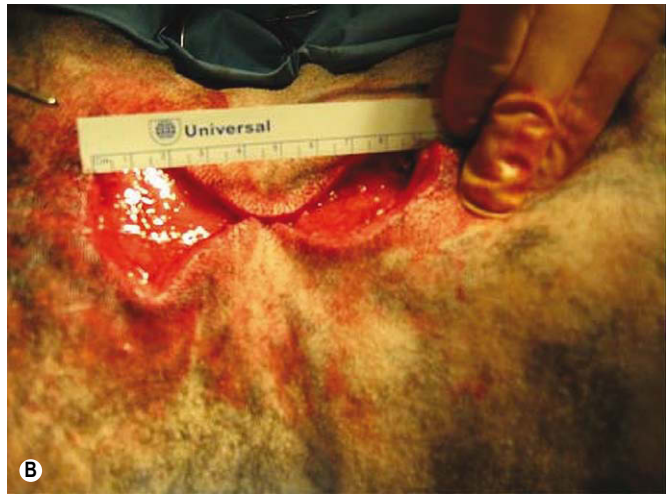
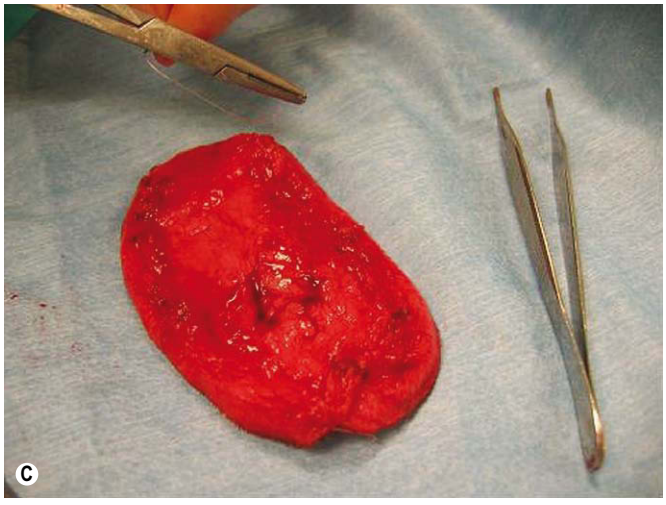


Figure 5.6 Scar on lateral chest from incomplete resection of a grade II soft tissue sarcoma. This scar and associated Penrose drain holes were removed with wide margins and the defect was closed primarily. Clean margins were obtained. Had the surgery been planned more carefully at the first attempt, a second surgery with attending morbidity and cost could have been avoided.







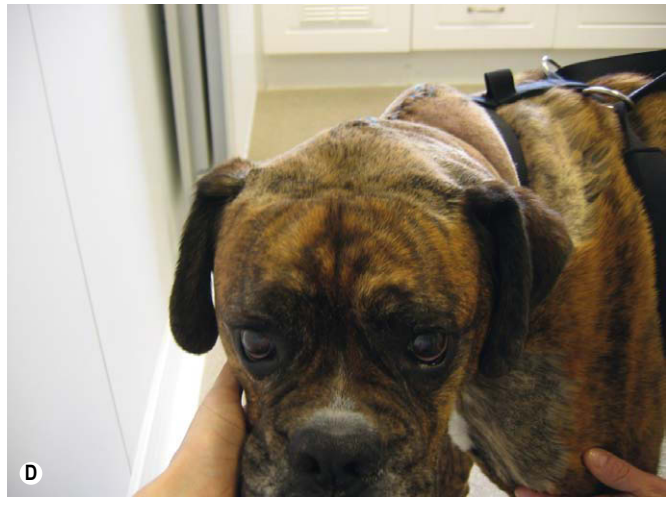


Figure 5.5 Obtaining wide surgical margins. (**A**) Mast cell tumour diagnosed on FNA cytology of unknown grade on dorsal neck of a Boxer dog. 2 cm lateral margins measured with sterile ruler and drawn with a sterile pen. (**B**) Removal with wide (2 cm) margins laterally and panniculus muscle on deep aspect (fascial layer). (**C**) Tacking the underlying fascial layer to the skin prior to immersion in formalin so that it resembles in situ status more closely so fascial planes do not 'slip' and artifactually expose tumour pseudocapsule, allowing accurate histopathological margin assessment. (**D**) Healed wound.

The deep margin is often the 'dirty' margin (**Figure 5.7**). Wide margins must include wide lateral (2–3 cm) and deep margins. A layer of fascia, if available, should be removed en bloc with the tumour as part of the deep margin. Fascial planes are relatively good biological barriers to tumour invasion. However, if the tumour is fixed to the underlying fascial layer, tumour cells can be assumed to be invading this tissue and the surgeon should remove a second, deeper fascial plane to achieve 'clean' margins.

A note on margin assessment

Ink for marking margins on resected specimens to assist histopathological margin analysis is useful. Submitting resected specimens in their entirety will also assist the assessment of margins by the pathologist, so invest in some large closed containers, rather than submitting small pieces of resected specimens making assessment of completeness of excision difficult. The tissue can be fixed in 10:1 formalin to tumour volume for 24–48 hours then submitted to the pathologist wrapped in gauze and double sealed in 'zip-lock' plastic bags. Another technique is submission of a separate margin of deep or lateral tissue. If the pathologist finds cancer in the submitted margin, then the surgery was an incomplete resection.

Surgery for palliation

This is to improve the patient's quality of life (to relieve pain and suffering or to improve function), but may not extend the life span. 'Treatment of any kind should never be worse than no treatment' (Withrow 2007). In other words, 'Do no harm'. However, this decision is often not black and white. The client and the veterinarian must consider the welfare of the animal the primary concern, i.e. morbidity versus the expected gain.

Surgery for debulking

This is used to remove the majority of (but not all of) the cancer to aid other treatment options (e.g. cryosurgery, chemotherapy, radiotherapy). This should be planned prior to surgery, and not used to try to salvage poor surgery.

Multimodal therapy (surgery plus chemotherapy/radiotherapy)

The surgical oncologist must have an understanding of the ways other cancer therapies can be combined with surgery. The surgical dose may be reduced significantly if radiotherapy and surgery are combined. Pre-, post- or intraoperative radiotherapy may be used but the choice depends on the combined thoughts of the radiation and surgical oncologist depending

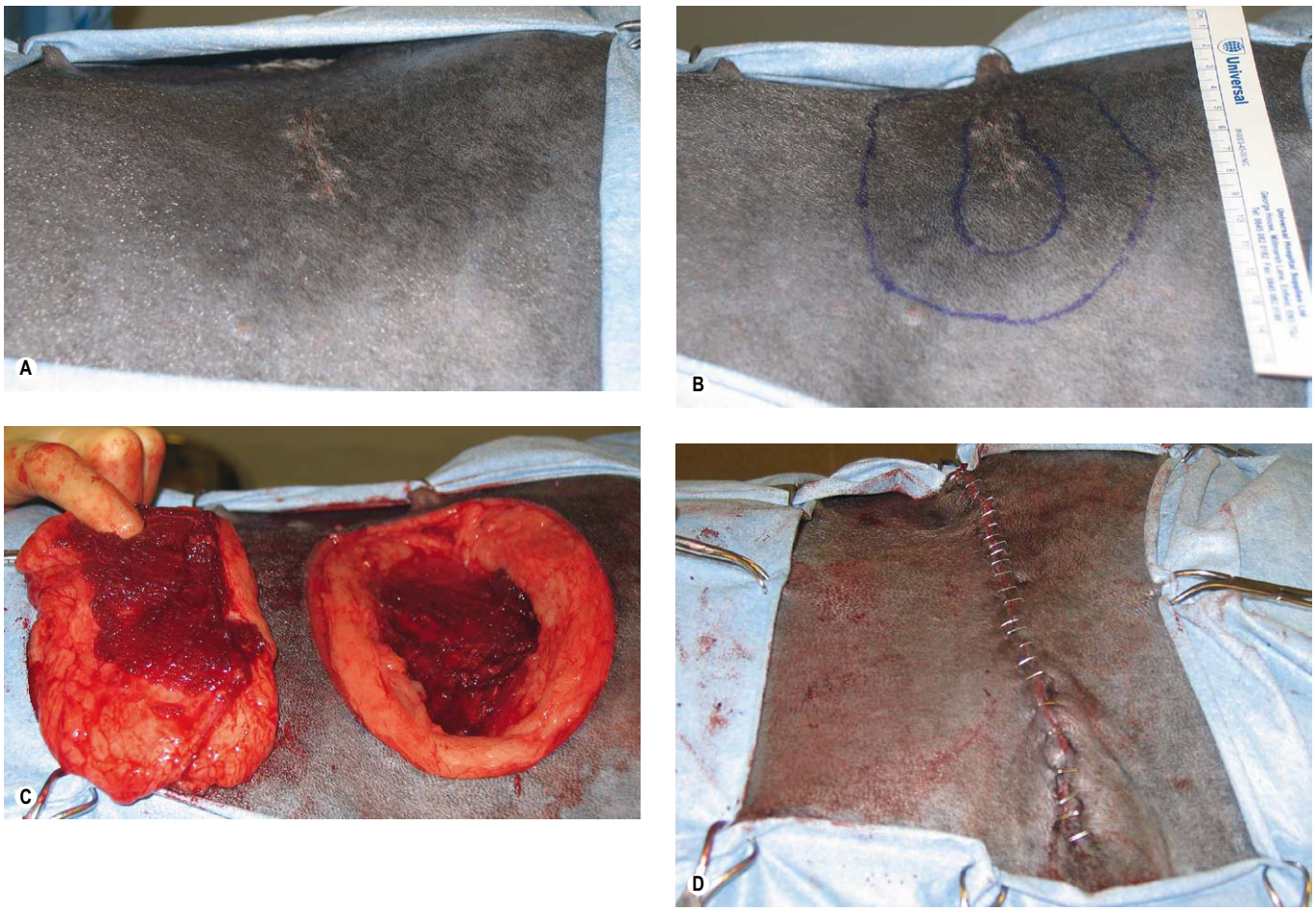


Figure 5.7 Resection of 'dirty' margins. (**A**) Scar of previous dirty resection of intermediate grade mast cell tumour on lateral trunk. (**B**) Wide margins of 3 cm laterally measured with sterile ruler and drawn with a sterile pen. (**C**) Note wide deep margin below the fascial layer, including part of underlying muscle. (**D**) Wound closed.

on the particular case. The prognosis for the patient and the control of its cancer may be improved with the combination of surgery and chemotherapy (e.g. amputation and chemotherapy for primary appendicular osteosarcoma). In some cases, surgery and radiotherapy and chemotherapy are all combined.

Surgery for cancer prevention

The development of mammary tumours in the dog is hormone dependent, and the risk of developing mammary tumours in dogs is reduced 200-fold by ovariohysterectomy <1 yr of age. Castration in the male dog will prevent testicular tumours and perianal adenomas. Removal of actinic keratitis (precancerous SCC) on poorly pigmented skin of dogs and cats may prevent progression to SCC. Removal of rectal adenomatous polyps may prevent progression to rectal adenocarcinoma. Retained (cryptorchid) testicles are at a high risk of malignant transformation, and so should undergo preventative, elective removal.

Further imaging of local disease to assist in surgical planning

Further imaging of local disease can assist in surgical planning. Radiography, CT, MRI and ultrasonography can all be used to plan the surgical removal of the local tumour and to assess feasibility of surgery (see Chapter 3).

Surgery and cancer staging

The oncology surgeon needs to be aware of the biological behaviour of the cancer under investigation. Do not miss the opportunity to obtain biopsies of other organs if they will help assess the extent of tumour progression within the animal. For example, if the surgeon removes a pancreatic insulinoma, biopsies should be taken of the most common potential metastatic sites (liver and lymph node) at the time of exploratory celiotomy to remove the primary mass. Proper staging is often a large part of the cancer surgeon's role, and knowledge of stage can greatly influence the prognosis and further treatment options (see Chapter 3).

Facilities/instruments

Electrocautery is a valuable tool for large resections. Closed suction drains are essential for large reconstructive flaps. A sterile ruler and pen are useful to mark out planned surgical margins accurately, and to plan reconstructive flaps (Pavletic 1999). Sterile suction facilities can be important for visualization for some surgeries such as removal of bleeding abdominal masses.

Surgical oncology cases requiring 'big' surgeries should be catered for in and out of the operating room. Facilities and staffing should reflect this. Specialist anaesthesia may be required. Administering appropriate levels of perioperative analgesia is of great importance, as is the anticipation of blood loss and the ready access to blood transfusions. The surgeon should also consider nutrition and the placement of feeding tubes.

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Principles of chemotherapy

The treatment of cancer usually is a multimodality approach, potentially involving surgery, chemotherapy, radiotherapy or a combination of two or more of the above.

In order to select the correct treatment options for each patient it is important to know the following:

- Histological diagnosis
- Stage of malignancy for which treatment is being considered
- Any concurrent medical problems.

For each patient a minimum database is required:

- Blood work (biochemistry and haematology)
- Urinalysis
- Radiographs as indicated.

For full staging, other diagnostics may be necessary, e.g. ultrasound/contrast studies, and the appropriate diagnostics will be discussed in specific chapters. Defining the stage is imperative in being able to predict prognosis. In addition, concurrent disease may influence the oncologist's choice of drugs, e.g. the use of lomustine in patients with liver disease. Once a diagnosis has been made it is important to define the goals and expectations of treatment.

Goals and expectations of treatment

Remission versus palliation

In many veterinary patients the goal is to achieve a complete remission, typically in patients with lymphoma. It is important to realize that a complete remission means that there is no visible sign of the tumour, not that all the cancer cells have been eliminated. This means that at some point the cancer will recur and, when it does, drug resistance may have occurred. In some cases (e.g. osteosarcoma), the goal is to prolong median survival time whilst informing the client that eventually the cancer will return in the form of metastatic disease. When chemotherapy is used in this fashion it is known as adjuvant therapy and treatment is targeted at micrometastatic disease. The third situation is where chemotherapy is being used to shrink a tumour in an attempt to improve quality of life without any possibility of a remission (e.g. large metastatic mast cell tumours) and is described as palliative therapy. In some instances chemotherapy may be used in an attempt to shrink a tumour prior to surgery (neo-adjuvant treatment).

Expected and potential side effects of treatment

It is the responsibility of the veterinary surgeon to fully understand the potential side effects of the drugs they intend to administer and when taking on that responsibility ensure that they have the facilities to provide adequate 24-hour care. Side effects can be acute (vomiting/diarrhoea), cumulative (bone marrow suppression) or idiosyncratic (haemorrhagic cystitis with cyclophosphamide).

Quality of life for the patient

It is the goal of every veterinary oncologist to give the cancer patient the greatest quantity of life without compromising the quality of that life or the bond between the client and their beloved companion.

Realistic expectation as to survival time for an individual

Statistics on median survival times for the most common veterinary cancers are known, e.g. lymphoma (see Chapter 22) and osteosarcoma (see Chapter 21). With some cancers that occur less frequently a lot of data is unavailable, and the expertise and experience of the clinical oncologist are required to assess the balance between risk and benefit of chemotherapy in the individual. It is important to remember that every patient is an individual and that many factors can influence overall survival times, not least being signalment, stage of disease, concurrent medical problems and the protocol selected.

What are the indications for the use of chemotherapy?

Chemotherapy is primarily given systemically in small animals. The major indications are:

- most effective single therapy for some malignancies, e.g. lymphoma and leukaemia (however, in certain cases, radiotherapy may be the treatment of choice)
- adjuvant treatment for highly metastatic tumours after surgery, e.g. osteosarcoma (OSA)
- shrinkage of large tumours prior to surgery or to relieve pain due to the large size of a tumour, when no other treatment is considered or practical (invariably, radiotherapy is the superior option in such cases)
- radiation sensitization – certain chemotherapeutics act synergistically with radiation to improve cell kill.

Rarely in veterinary medicine chemotherapy will be given intralesionally (Yoshida et al 1998) or intracavitary (Moore et al 1991) for tumours where systemic administration is unlikely to result in a high enough concentration of drug reaching the target.

Once the decision to treat has been made, the next step is selection of protocol. There are a number of cytotoxic drugs used in the treatment of canine and feline cancers and more and more drugs are becoming available to the veterinary oncologist. Selection of appropriate drugs depends on species, type of cancer, availability, experience of the veterinary surgeon, facilities to handle these drugs and the cost.

Many sources are available to obtain dosages for the better-known drugs. It is important that drugs are administered at the optimal time interval. If they are given too close together then significant toxicity can result, especially if the toxicities of the drugs overlap. Alternatively, if the drugs are given too far apart, tumour cells have time to develop resistance and repopulate. It is known that the repair enzymes of tumour cells are not as efficient as those of normal cells, and, therefore, it is possible to capitalize on this by scheduling treatments such that normal cells have had time to repair but the cancer cells have not. However, it is important that the patient is well enough to receive treatment; if in any doubt, a short delay may be necessary.

What are the principles on which chemotherapeutic protocols are derived?

Combination protocols

Combinations of drugs provide maximum tumour cell kill whilst limiting individual drug toxicity. Utilization of drugs that have different mechanisms of action means that resistance within a heterogeneous population will develop more slowly. Tumours that are large enough to be detected ($>10^6$ cells) are a heterogeneous population containing drug-resistant clones (Goldie et al 1982). This means that with single-agent protocols response will be short because of the rapid repopulation with resistant cells.

Drug selection is based on proven efficacy of the drug against the tumour in question and the ability to give it at consistent intervals; the treatment-free interval between cycles should be the shortest time possible for the recovery of the most sensitive normal tissue, usually the bone marrow. The storage compartment of the bone marrow is able to supply mature cells for ~10 days after the stem cell pool has been damaged. This means that what is seen in the peripheral blood is about a week behind what is going on in the marrow.

The nadir of leucopenia exhibited by the various drugs is an important consideration in chemotherapy protocols. All drugs should be given at their optimal dose and schedule. When several drugs of a class are available, the drug selected should not have overlapping toxicities with other selected drugs. In some instances, however, single agents are used as the overall survival times with combination protocols have not been shown to be superior to single agents but the toxicity is significantly greater, e.g. doxorubicin in the management of splenic haemangiosarcoma (see Chapter 23).

Fractional kill hypothesis and tumour cell number

There is an inverse relationship between the total number of neoplastic cells and 'curability'. Early diagnosis and early treatment give the patient the best possible prognosis. The same percentage of cells is killed per cycle of a given drug, irrespective of the number of cells. This is known as the fractional kill hypothesis and each cycle of treatment will kill a specific fraction of the remaining cells. The objective of each cycle is to reduce the absolute number of remaining cells due to the cumulative effect of successful fractional kills.

Pharmacological principles

The pharmacokinetics of chemotherapeutic agents is important as this examines the distribution of drugs and their metabolites throughout the body and ultimately the bioavailability of drugs to kill cancer cells and therefore their therapeutic effect (Ehrlichman 1992). Intravenous administration assumes 100% bioavailability but administration via other routes (oral, intramuscular, subcutaneous) may only be partial. It is important to remember that the bioavailability of many chemotherapeutic drugs used in veterinary oncology that are not given i.v. will not have had their bioavailability validated.

A number of factors influence the distribution of drugs within the body and include blood flow to different organs, diffusion of drug from blood vessels, protein binding and lipid solubility. Doxorubicin shows extensive tissue binding and therefore has slow release of the drug from these sites. A drug such as carmustine (BCNU) that is lipid soluble, and therefore penetrates the blood–brain barrier, should also have a slow elimination phase; however, it is inactivated quickly, meaning that there is only a very short exposure of body tissues to the drug.

Peak plasma concentration versus concentration over time

The cytotoxic effect depends on concentration over time, whereas toxicity to normal tissue depends on peak plasma concentration.

Therapeutic index

Therapeutic efficacy is based on giving the maximum amount of drug that causes minimal toxicity. For most chemotherapeutics the margin between therapeutic dose and toxicity is narrow and care must be taken to administer these drugs accurately. Drug dosages are usually calculated as mg/m^2 or mg/kg (see Tables 6.8 and 6.9 at the end of this chapter). When calculating doses using the m^2 chart, it is important to remember that a small dose reduction may be required in small dogs and in older patients where the bone marrow is not as resilient.

Cell cycle

The cell cycle (**Figure 6.1**) is important when putting together a chemotherapy protocol and drugs can be broadly classified into those that affect a particular point in the cell cycle, known as cell-cycle specific, e.g. the vinca alkaloids, and those that

can act on the cell at any time during the cell cycle, non-cell cycle specific, e.g. alkylating agents.

Classification of drugs

Chemotherapeutics are classified both by their mechanism of action and their chemical structure. A discussion of some of the cytotoxic drugs most commonly used in veterinary medicine follows; this is by no means an exhaustive list and for further details concerning these drugs and other cytotoxics not listed here, reference to a more advanced text is recommended. Tables 6.1–6.6 describe the major groups of drugs, the most frequently used members of the group, known mechanism of action, method of excretion and some of the more commonly seen side effects; this is not a complete description of the drugs but rather a guideline.

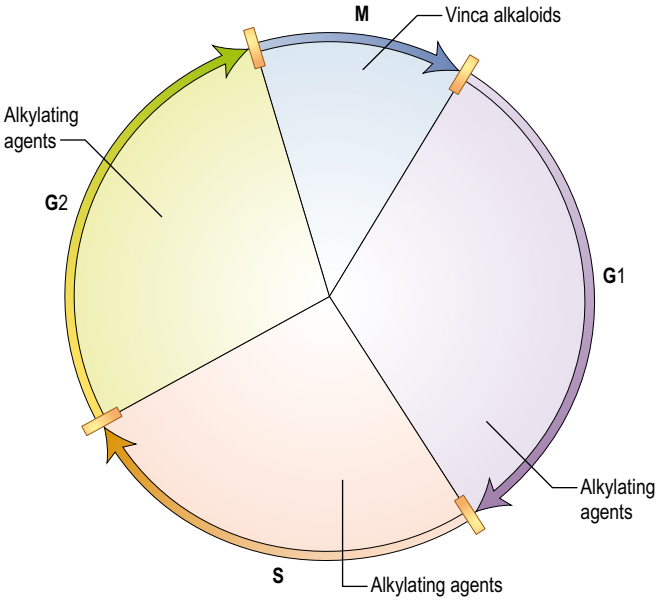

Figure 6.1 The cell cycle. G1, RNA and protein synthesis; S, DNA synthesis; G2, RNA and protein synthesis; M, mitosis.

Balancing toxicities

Chemotherapeutic agents are targeted at rapidly dividing cells and therefore preferentially target neoplastic cells; however, rapidly dividing normal cells are vulnerable to the effects of these drugs. Primarily we think of the bone marrow and gastrointestinal tract as the most vulnerable so it is important, when possible, to balance toxicities such that two very myelosuppressive drugs are not used in tandem when a less myelosuppressive drug is available, e.g. the balance of vincristine with cyclophosphamide.

What are the most frequently reported toxicities and how should they be handled?

Haematological

The bone marrow is susceptible to damage from chemotherapeutic agents because of its high growth fraction. In the majority of cases neutrophils are primarily affected, followed by platelets. In patients on long-term chemotherapy, anaemia may result, but this is usually mild and rarely significant.

Neutropenia is commonly encountered during chemotherapy and is the most common dose-limiting toxicity. The nadir

Table 6.1A Key features of alkylating agents

	Cyclophosphamide (Endoxana, Cytoxan)	Chlorambucil (Leukeran)	Melphalan (Alkeran)	Ifosfamide
Mechanism of action	Alkylation of DNA	Alkylation of DNA	Alkylation of DNA	Alkylation of DNA
Metabolism	Microsomal hydroxylation to active form, hydrolysis to acrolein, excretion as inactive products	Chemical decomposition to active and inactive products	Chemical decomposition to inert products	As other alkylating agents
Principal toxicities	Myelosuppression, platelets spared, sterile haemorrhagic cystitis, alopecia	Platelets affected	Myelosuppression (delayed nadir 4–6 weeks)	Myelosuppression Severe haemorrhagic cystitis can result with this drug – uroprotect with 2-mercaptoethanesulfonate (MESNA)
Precautions	Tablets should not be divided Appropriate handling of lyophilized powder within a safe environment is necessary	Tablets should not be divided	Tablets should not be divided	As for other alkylating agents
Drug dosage	Dogs: 200–250 mg/m^2 Cats: 10 mg/kg	Dogs: 0.1–0.2 mg/kg once daily (individual protocols vary, so check protocol carefully before prescribing) Cats: 2 mg every other day	Dogs: 0.1 mg/kg daily for 10 days then 0.05 mg/kg daily	Dogs: 350–375 mg/m^2 i.v. q 3 weeks
Indications	Lymphoma, leukaemia, multiple myeloma, plasmacytomas	Chronic lymphocytic leukaemia, lymphoma, multiple myeloma	Multiple myeloma, lymphoma	No proven advantage over cyclophosphamide Sterile haemorrhage cystitis is a concern

Table 6.1B Key features of other alkylating agents

	CCNU (Lomustine, CeeNU)	BCNU (Carmustine)	Busulphan
Mechanism of action	Nitrosourea alkylates DNA and RNA Not cross resistant with other alkylating agents	Nitrosourea Alkylates DNA as lomustine	Alkylating agent
Metabolism	Metabolized by the liver Active metabolites excreted via kidneys	As for lomustine	Metabolized to several products and excreted in the urine
Principal toxicities	Myelosuppression can be severe especially at higher doses and is dose limiting Hepatic, renal	Myelosuppression can be severe Nausea, vomiting	Bone marrow suppression (myelosuppression and thrombocytopenia) can be prolonged
Precautions	Consider dose reduction in patients with hepatic/renal disease	Associated with pulmonary fibrosis in humans	Tablets should not be divided See also other alkylating agents
Drug dosage	Dogs: 60–90 mg/m^2 p.o. Cats: 50 mg/m^2 p.o.	Dogs: 50 mg/m^2 i.v. every 6 weeks	Dogs: 2 mg/m^2 p.o.
Indications	Lymphoma, mast cell tumours, histiocytic sarcomas in combination with radiotherapy, and gliomas	Rarely used in veterinary medicine, but does cross the blood–brain barrier	Chronic myelogenous leukaemia

Table 6.1C Features of non-classic alkylating agents

Drug	Procarbazine (Matulane)	Dacarbazine (DTIC)
Mechanism of action	Alkylation of DNA	Exact mechanism is unknown but at least in part acts as an alkylating agent
Metabolism	Metabolised by the liver, excreted by the kidney as inactive metabolites	Drug is eliminated by renal tubular secretion and extensively metabolized in the liver
Principal toxicities	Leucopenis and thrombocytopenia-late onset	Myelosuppression, hepatotoxicity, anorexia, nausea, vomiting, alopecia, anaphylaxis
Precautions	Oral-capsules should not be divided	Vesicant if extravasated. Incompatible with hydrocortisone sodium succinate
Drug dosages	Dogs 50 mg/m^2 daily for 14 days (MOPP protocol)	Dogs 200 mg/m^2 iv as a slow bolus. Day 1–5 or every 3 weeks in combination with doxorubicin or CCNU
Possible Indications	Rescue protocols for lymphoma	Rescue protocols for lymphoma

Table 6.2 Key features of vinca alkaloids

	Vincristine (Oncovin)	Vinblastine	Vinorelbine
Mechanism of action	Inhibits polymerization of tubulin	Inhibits polymerization of tubulin	Semisynthetic derivative of vinblastine
Metabolism	Hepatic with biliary excretion	Hepatic with biliary excretion	As with other vinca alkaloids
Principal toxicities	Ileus, constipation, peripheral neuropathy	Neutropenia, thrombocytopenia	Neutropenia; peripheral neuropathy greater than vincristine, constipation
Precautions	Vesicant if extravasated	Vesicant – care with catheter placement	As for other vinca alkaloids
Drug dosage	Dogs: 0.5–0.75 mg/m^2 Cats: 0.025 mg/kg or 0.75 mg/m^2	Dogs and cats: 2 mg/m^2 as per protocol	Dogs: 15–18 mg/m^2 i.v. weekly
Indications	Leukaemias, lymphomas, some solid carcinomas and sarcomas, mast cell tumours	Lymphomas, leukaemias, mast cell tumours	Rarely used in veterinary medicine

Table 6.3 Key features of anti-tumour antibiotics

	Doxorubicin (Adriamycin)	Epirubicin	Mitoxantrone (Novantrone)	Actinomycin D (Cosmegan, Dactinomycin)
Mechanism of action	Pleiotropic effects: • inhibition of DNA topoisomerase II activity • free radical damage • apoptosis and others	Pleiotropic effects: • inhibition of DNA topoisomerase II activity • free radical damage and others	Inhibits topoisomerase II	Antitumour antibiotic
Metabolism	Doxorubicinol major metabolite 50–60% of parent drug accounted for by known routes of elimination, mostly biliary Can bind to DNA and cardiolipin in tissue and is slowly dissociated	Primarily parent compound drug accounted for by known routes of elimination, mostly biliary	Primarily excreted by the liver	Excretion through urine and faeces
Drug interactions	Binds heparin and forms aggregates	Incompatible with heparin	Incompatible with heparin	–
Principal toxicities	Myelosuppression (nadir 7–10 days), gastrointestinal, alopecia, cardiac Severe local tissue damage if extravasated Allergic reactions	As for doxorubicin More gastrointestinal side effects have been seen with epirubicin	Myelosuppression (nadir 7–10 days) Fewer gastrointestinal and allergic reactions	Myelosuppression, gastrointestinal (nausea and vomiting)
Precautions	Ensure i.v. catheter is securely placed to prevent extravasation Dose-related cardiomyopathy, radiation recall, possible dose reduction with severe hepatic disease	Vesicant if extravasated	Mild vesicant	If extravasated will cause pain, swelling and necrosis
Drug dosage	Dogs: 30 mg/m^2 every 3 weeks Cats: 1 mg/kg every 3 weeks	As with doxorubicin	Dogs: 5.0–5.5 mg/m^2 every 3 weeks Cats: 5.0–6.5 mg/m^2 every 3–4 weeks	Dogs: 0.5–0.7 mg/m^2
Indications	Leukaemias, lymphomas, carcinomas (mammary), sarcomas (haemangiosarcoma) – wide range of activity	Substitute for doxorubicin Cardiac toxicity has been reported and this drug should *not* be used in patients with pre-existing heart conditions	Squamous cell carcinoma, lymphoma, transitional cell carcinomas Substitute for doxorubicin	Salvage drug for patients with lymphoma May be beneficial for patients with acute lymphoblastic leukaemia

Table 6.4 Key features of platinum compounds

	Cisplatin (Platinol)	Carboplatin (Paraplatin)
Mechanism of action	Covalently binds to DNA	Covalently binds to DNA
Metabolism	Inactivated intracellularly Elimination: 26% excreted in first 24 hours; >90% renal excretion	90% excreted in urine in 24 hours
Principal toxicities	Nephrotoxic, nausea/vomiting, myelosuppression, ototoxicity, peripheral neuropathy, hypersensitivity, seizures Pulmonary oedema in cats	Myelosuppression, nausea/vomiting Possible nephropathy in patients with prior renal disease
Precautions	Aggressive diuresis and anti-emetic therapy necessary Maintain high urine flow during therapy Monitor BUN/creatinine and urine for casts before each treatment Do not administer with other nephrotoxic drugs (e.g. NSAIDS or aminoglycosides)	Diuresis is recommended before treatment in patients with history of renal disease Monitor renal parameters
Drug dosage	Dogs: 50–70 mg/m^2 *Fatal in cats*	Dogs: 300 mg/m^2 Cats: 180–210 mg/m^2
Indications	Osteosarcoma, intracavitary mesothelioma, carcinomatosis, squamous cell carcinoma Radiosensitizer for nasal tumours	Osteosarcoma, squamous cell carcinoma Intracavitary, radiosensitizer

Table 6.5 Key features of antimetabolites

	Cytarabine (Cytosar-U, Ara-C), cytosine arabinoside	Methotrexate	Gemcitabine
Mechanism of action	Inhibits DNA polymerase-a Is incorporated into DNA and terminates DNA chain elongation	Inhibition of dihydrofolate reductase leads to partial depletion of reduced folates	Analogue of deoxycytidine Active metabolite is incorporated into DNA Has similarities to Ara-C
Metabolism	Less than 10% of the drug is eliminated in the urine unchanged	Excretion primarily as intact drug in urine	75% of the drug is excreted in the urine within 24 hours
Principal toxicities	Leucopenia, anaemia, vomiting, diarrhoea	Myelosuppression (nadir 6–9 days) Mucositis, gastrointestinal epithelial denudation, vomiting/anorexia, hepatotoxicity, renal toxicity, alopecia	Myelosuppression, gastrointestinal
Precautions	Incompatible with heparin	Should not be given with NSAIDs as they reduce renal secretion of methotrexate and may increase toxicity Also do not combine with sulphonamides or tetracyclines due to potential increased toxicity	–
Drug interactions	Synergistic with L-asparaginase; may be antagonistic with methotrexate	NSAIDs reduce renal clearance and increase toxicity L-asparaginase blocks toxicity and anti-tumour action 'Leucovorin' rescue	–
Drug dosage	Cats: 100 mg/m^2 s.c. every 6–8 hours for 3–4 injections every 6–9 days, or 10 mg/m^2 s.c. every 12 hours Dogs: 600 mg/m^2 s.c. divided into two doses 24 hours apart, or constant rate infusion of 100 mg/m^2 i.v. per 24 hours for 3–4 days	0.5–0.8 mg/kg i.v. p.o.	Dogs: 400 mg/m^2 i.v. infusion weekly for 3 weeks
Indications	Lymphoma, especially CNS, Granulomatous meningo encephalitis (GME)	Lymphoma, transmissible venereal tumour, myeloproliferative disorders	Gastric carcinoma

Table 6.6 Key features of other cytotoxic drugs

	L-asparaginase	Hydroxyurea (Hydrea)
Mechanism of action	Depletion of essential amino acid asparagines, therefore inhibition of protein synthesis	Inhibits the enzyme ribonucleotide reductase
Metabolism	Proteolytic degradation	50% of the drug is metabolized by the liver to inactive compounds and the remainder excreted unchanged by the kidneys
Principal toxicities	Decreases protein synthesis Pancreatitis, anaphylaxis hypersensitivity Increased liver enzymes	Myelosuppression Paronychitis Gastrointestinal (vomiting, diarrhoea)
Precautions	Use with caution in patients with hepatic disease or pancreatitis	Contraindicated in patients with severe renal dysfunction
Drug dosage	Dogs: 400 IU/kg i.m. or 10,000 IU/m^2 i.m. Cats: 400 IU/kg	Dogs: 50 mg/kg p.o. sid or divided bid then every other day Cats: 10 mg/kg sid then every other day
Indications	Lymphoma	Chronic myelogenous leukaemia Polycythaemia Very synergistic with radiation

of neutropenia for most of the common drugs is 7–10 days, and rebound will usually occur within 4–5 days after the nadir is reached. It is important that the white blood cell (WBC) count is checked on any chemotherapy patient prior to treatment. In many instances the neutropenia is mild and will not affect treatment. However, in patients with very low counts (<3.0 10^9/l), a delay in treatment is necessary and a repeat blood count taken before continuing with chemotherapy. If the patient is clinically well and has no signs of fever, then antibiotics are not required; however, close monitoring is necessary in these patients.

Any patient with a low absolute neutrophil count and fever requires antibiotics; if the count is very low (<1.5 10^9/l), then hospitalization for supportive care and intravenous administration of antibiotics is required. In patients that have severe neutropenia (<1.5 10^9/l), but are clinically well, treatment delay and the administration of a broad-spectrum antibiotic is indicated.

Severely neutropenic and potentially septic patients constitute a true oncological emergency (see Chapter 9) and, when possible, the location of the source of sepsis should be determined. Any chemotherapy patient that is lethargic, weak or anorexic should be evaluated by a veterinary surgeon as an emergency. Common sources of infection include bacterial translocation from the gastrointestinal tract due to damage of the mucosal surface after chemotherapy, urinary tract infections and pneumonia. If a potential source of infection is located, a sample for culture should be submitted.

In addition to antibiotics and supportive care, granulocyte-colony stimulating factor (G-CSF) can be administered to stimulate the neutrophil count. Practically in veterinary oncology it is rarely used. It is a human recombinant product and therefore prolonged use would be contraindicated due to the possibility of induction of cross-reactive antibodies to the endogenous G-CSF. It is not recommended for afebrile patients or prophylactically, and the 3–5 day delay before the effects of treatment are seen means that in many cases the bone marrow would have already responded adequately without intervention. In those patients where G-CSF is appropriate, one or two doses s.c. at 2.5–10 g/kg should result in an improvement in neutrophil count.

If a patient has experienced severe neutropenia after treatment, then a dose reduction of 10–20% (depending on the extent of the problem encountered) is necessary; if the patient still encounters a problem, then a change in chemotherapeutic would be advisable.

Vomiting

This is a fairly commonly reported side effect of chemotherapy and may result from a direct effect of the drug on the vomiting centre or the chemoreceptor trigger zone (CRTZ). Vomiting can occur acutely (within 8 hours), most notably with the platinum drugs, or more usually 2–5 days after treatment (doxorubicin).

The mechanism by which chemotherapeutic agents cause vomiting is complex (**Figure 6.2**). The vomiting centre is responsible for the motor mechanisms of emesis and receives input from the CRTZ, vestibular system and the gastrointestinal tract. Receptors located within the vomiting centre include H_1, muscarinic and 5-HT_3. The CRTZ is located in the medulla, outside of the blood–brain barrier, and receives chemical information from the body. Receptors located within this region include D_2 and 5-HT_3. The gastrointestinal tract sends impulses to the brain along the vagus nerve, with some input from the splanchnic nerves. Receptors include 5-HT_3. The cortex may be important in anticipatory vomiting.

In the majority of cases, acute vomiting from chemotherapy is self-limiting. In those patients with persistent vomiting, anti-emetics and supportive care may be required (Table 6.7). With any side effect of treatment it is important to discontinue treatment until the patient is well and eating normally. It is advisable to give a prophylactic anti-emetic (metoclopramide or Maropitent citrate) after chemotherapy, and/or a reduction in dose may be necessary.

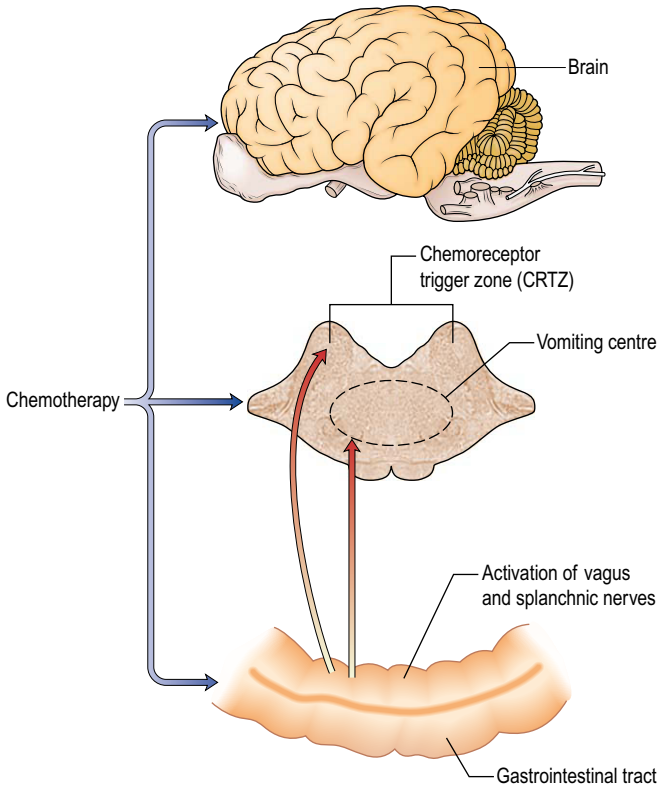

Figure 6.2 Pathways involved in chemotherapy-induced emesis.

Diarrhoea

As with vomiting, diarrhoea is a relatively common side effect of chemotherapy and in the majority of cases is self-limiting. In some instances, however, especially with doxorubicin, diarrhoea can be severe and may require hospitalization for supportive care (fluid therapy and antibiotics if severe to prevent bacterial translocation). A bland diet is recommended until the diarrhoea resolves, and treatment should be delayed until the patient is clinically well. In cases of severe diarrhoea (e.g. with doxorubicin), a dose reduction is indicated.

Alopecia

The extent of alopecia seen in veterinary medicine is breed dependent and is most severe in dogs with continually growing hair coats such as Poodles, Bichon Frises (**Figure 6.3**) and Old English Sheepdogs. Terriers, Lhasa Apso and Shih Tzu may also have significant hair loss, particularly on the face; dogs with 'feathers' on the legs may lose these and there may be some change in hair coat without significant hair loss. Areas that have been shaved may be slow to regrow and whiskers will fall out. Drugs most likely to cause the most severe hair loss are doxorubicin and cyclophosphamide.

Allergic reactions

Idiosyncratic allergic reactions can occur with any chemotherapeutic agents; however, L-asparaginase and doxorubicin are the agents most commonly associated with hypersensitivity reactions. Typical signs include head shaking, urticaria, erythema, restlessness, vomiting and oedema. With a severe

Table 6.7 Anti-emetics in veterinary oncology

Drug	Site of action	Indications	Dose
Metoclopramide (substituted benzamide)	Central: at high doses has both anti-dopaminergic and anti-serotonergic effects Works on both the CRTZ and the vomiting centre Peripherally increases lower oesophageal sphincter tone and relaxes the pylorus Contraindicated in patients with gastrointestinal obstruction	Most commonly used anti-emetic and good for mild/moderate vomiting	0.2–0.4 mg/kg p.o. tid/qid 1–2 mg/kg/day constant rate infusion
Maropitant citrate (Cerenia)	Blocks NK-1 receptor in the emetic (vomiting) centre	Currently a new drug licensed for both peripheral and central causes of vomiting	Injectable: 1 mg/kg s.c. sid Tablets: 2 mg/kg sid (Both formulations are bioequivalent and may be used interchangeably for up to 5 days)
Phenothiazines (e.g. chlorpromazine)	Central (CRTZ) dopamine antagonists	Effective for mild nausea	0.5 mg/kg i.m. or s.c. tid/qid
Butorphanol	Opioid agonist/antagonist Thought to exert its effect at the level of the vomiting centre	Used primarily prior to cisplatin chemotherapy	0.2–0.6 mg/kg s.c. i.m.
Serotonin antagonists (e.g. ondansetron)	Inhibit the 5-hydroxytryptamine (5-HT) receptor in the CRTZ	Indicated in all patients with severe vomiting	0.1–0.5 mg/kg i.v. or p.o. bid Up to 1 mg/kg can be given orally

CRTZ, chemoreceptor trigger zone.

Figure 6.3 Bichon Frise showing (**A**) doxorubicin-induced alopecia and (**B**) subsequent regrowth of hair once treatment finished.

reaction, hypotension may result, leading to collapse. The authors advise pre-treatment of patients with chlorphenamine (Piriton) prior to doxorubicin chemotherapy. Repeated treatments with L-asparaginase are more likely to result in hypersensitivity reactions.

Should an allergic reaction occur, stop treatment and treat with either diphenhydramine 0.2–0.5 mg/kg i.v. slowly, or chlorphenamine 2.5–10 mg i.m. and dexamethasone sodium phosphate 0.5–2 mg/kg i.v. Rarely intravenous fluids and adrenaline (epinephrine) are required.

Extravasation

All chemotherapy drugs should be administered via an aseptically placed intravenous catheter. It is essential to ensure that the catheter is correctly placed and flushed well with saline both before and after administration of a drug. Many of these drugs will cause significant local damage if placed extravascularly. The major drugs in this category are doxorubicin, the vinca alkaloids and actinomycin D.

Nephrotoxicity

The drug most commonly associated with nephrotoxicity is cisplatin. This drug is used less frequently now with the ready availability of carboplatin. All patients given cisplatin must be diuresed with 0.9% NaCl before the drug is given. Saline is recommended because the toxicity of cisplatin is reduced in a high chloride environment. There are a number of protocols, but the authors will diurese for 6–8 hours on twice maintenance saline, following which cisplatin is given slowly i.v. over 45 minutes. The patient is pre-treated with dexamethasone 0.025 mg/kg i.v., butorphanol 0.1 mg/kg i.v. and chlorpromazine 0.5 mg/kg i.m. Immediately after administration of cisplatin, give 0.5 g/kg of mannitol i.v. and continue saline diuresis for a further 6–8 hours. Urinalysis (check for casts) and renal parameters should be checked before administration of cisplatin. *Cisplatin is fatal if given to cats*.

In patients with renal disease it is recommended to give saline diuresis for up to 4 hours before giving carboplatin; in patients with no renal impairment this is not necessary.

Doxorubicin has been reported as being nephrotoxic in cats and should be used with caution in cats with renal disease. Monitoring of renal parameters and urinalysis is important in such patients.

Neurotoxicity

Neurotoxicity is rarely seen in veterinary medicine. Drugs associated with neurotoxicity include vincristine, cisplatin and 5-fluorouracil. Seizures have been reported after administration of cisplatin, as have two cases of cortical blindness.

Vincristine may cause a peripheral neuropathy that can be difficult to detect. Hind leg weakness, tail chasing/chewing or abnormal behaviour that cannot be explained otherwise may be due to vincristine and in such patients the drug should be discontinued and vinblastine substituted. Paralytic ileus is a potential side effect of vincristine and is characterized by anorexia, abdominal pain, constipation and occasional vomiting. Patients will often make a spontaneous recovery after 24–48 hours. Supportive care in the form of intravenous fluids and pain management may be required. The effect can be cumulative, and if a dose reduction does not improve clinical signs, the drug should be discontinued. Chemotherapy should not be continued in any patient that is clinically unwell until the clinician is satisfied as to the cause of the problem. If it is a side effect of treatment, this must be resolved first to prevent making the patient even more unwell. Neurological signs resolve on stopping the drug.

5-Fluorouracil (5-FU) is contraindicated in cats because of severe neurological signs that can be fatal. Neurological signs can also develop in dogs and, although less severe, for this reason 5-FU is rarely used in canine patients.

Carcinogenesis

It is well to remember that cytotoxic drugs are potentially carcinogenic and may induce second cancers; this applies most particularly to alkylating agents such as cyclophosphamide. The incidence in veterinary patients is low, primarily because the majority of patients are middle-aged to older, but in younger patients that are expected to have a relatively normal life span the possibility for second tumours cannot be completely discounted, e.g. the development of transitional cell carcinoma in patients treated long-term with cyclophosphamide.

Hepatotoxicity

The drug most commonly associated with hepatotoxicity in veterinary medicine is lomustine (CCNU). All patients on long-term CCNU must have their liver function checked frequently. Should signs of hepatotoxicity arise, the drug should be discontinued. In patients with elevated liver enzymes, a bile acid stimulation test is advised before starting on CCNU. If the decision is made to go ahead with treatment, then close monitoring is advisable. This is an idiosyncratic response to the drug and may be more frequently encountered at higher doses.

Cystitis

Sterile haemorrhagic cystitis is a potential side effect of cyclophosphamide and a routinely encountered side effect of ifosfamide, such that the latter must be given in conjunction with 2-mercaptoethanesulfonate (MESNA) (Rassnick et al 2000). In the majority of cases it occurs after chronic use, but can occur acutely. Cystitis is the result of irritation of the mucosal surface of the urinary bladder by the metabolite acrolein. Clinical signs include haematuria that can be severe, pollakuria and stranguria. A urine culture should be submitted to rule out infection.

The treatment of choice is to stop cyclophosphamide immediately and start the patient on anti-inflammatory drugs; personally, the authors prefer prednisolone to NSAIDs. Most patients respond well to stopping treatment; however, it can take many weeks for symptoms to resolve. Further use of cyclophosphamide is contraindicated and another alkylating agent, e.g. chlorambucil, should be substituted. Other strategies to reduce the incidence of cystitis include giving furosemide with cyclophosphamide, ensuring that the patient has good access to water to facilitate elimination of acrolein. Further approaches include adding salt to the diet for 24 hours on the day of treatment and giving oral medication in the morning so as to reduce the likelihood of acrolein remaining in the bladder for an extended period of time (overnight).

Cardiac

Cardiotoxicity is primarily associated with the anthracycline antibiotic doxorubicin in the dog. In the majority of cases this is a cumulative toxicity that can result in dilatative cardiomyopathy, the end result of which is congestive heart failure. Acute toxicity can be seen by the development of arrhythmias that are usually transient.

The mechanism of toxicity is thought to be free radical damage to the myocardium. Cardiac tissue has relatively low levels of protective enzymes and is therefore vulnerable to oxidative damage. Examination of affected cardiac muscle is characterized by degeneration and atrophy of myocytes, cytoplasmic vacuolation and cell lysis. Dogs appear to be most susceptible to toxicity, with humans tolerating cumulative doses of 550 mg/m^2, whereas dogs should not exceed a cumulative dose of 240 mg/m^2. Practically, cumulative doses up to 210 mg/m^2 would be considered 'safe', providing there was no underlying cardiac disease (Mauldin et al 1992). Once clinical signs of cardiotoxicity develop it is irreversible and treatment is the same as for any patient with congestive heart failure; it is important, therefore, not to exceed the recommended dosage. Using the typical protocols incorporating doxorubicin in cats, cardiac toxicity has not been recognized, but one study did show damage to cardiac tissue if a total dose of 300 mg/m^2 was exceeded (O'Keefe et al 1993).

Early diagnosis would be beneficial but currently accurate screening is not available. It is anticipated in the future that screening for biomarkers such as cardiac troponins and atrial natriuretic peptide (ANP) will provide a way to monitor and diagnose toxicity.

To reduce the incidence of cardiotoxicity, all patients with a history of heart disease, or a breed with predisposition for dilatative cardiomyopathy, should have an echocardiogram before starting treatment. An ECG should be run before each treatment and development of an arrhythmia or changes in the QRS complex should prompt an echocardiogram.

Patients with heart disease should have another drug substituted for doxorubicin, e.g. mitoxantrone. A liposomal formulation of doxorubicin is available that is less cardiotoxic; however, availability is limited and it is expensive. Allergic reactions to the liposomes have also been encountered.

The use of cardiac protectants has been advocated and dexrazoxane has been shown to reduce cardiac toxicity in the dog; however, this is currently not available in the UK.

Safe handling of cytotoxic drugs

Staff

It is essential when working with chemotherapeutic agents to store, handle, dispense and dispose of them appropriately (Dickinson & Ogilvie 1995). All staff working with chemotherapeutics should be properly trained and be conversant with procedures should a spillage occur. Cytotoxics should be stored in a specially designated area and clearly labelled.

All chemotherapeutic agents should be handled in a biological safety hood. Wear appropriate safety clothing, eye protection, disposable gown and mask (**Figure 6.4**). Ensure that no skin comes into contact with the drugs being dispensed. Cover the work area with plastic-backed absorbent paper. All disposables should be disposed of in clearly labelled cytotoxic drug containers. Hands should be washed before and after handling chemotherapeutic agents.

For drugs that require reconstitution, venting devices, if available, should be used. If not, alcohol-soaked gauze pads can be used to decrease aerosolization. Under *no* circumstances should these drugs be reconstituted without a biological safety hood. In veterinary medicine the drugs to which this applies most commonly would be doxorubicin and cyclophosphamide. Always follow the manufacturers' instructions on the reconstitution of all drugs.

When administering drugs slowly by infusion, ensure that the catheter is placed aseptically and then flushed well with saline before and after administration of the drug.

The patient

- When administering drugs, always check the calculation (m^2 versus kg).
- When delivering drugs intravenously, place an indwelling catheter aseptically – do not administer directly off the needle.
- When dispensing, do *not* divide tablets containing cytotoxics – carefully calculate the total dose and then allocate whole tablets accordingly.

Figure 6.4 Preparation of cytotoxic drugs using an approved biological safety hood.

The client

All clients should be instructed on the potential side effects of chemotherapy. The safe administration of oral medications is essential for those patients sent home on cytotoxic drugs. Clients should be given gloves to ensure no contact with these agents. All cytotoxics should be clearly labelled and a small handout for the client to read can be extremely helpful.

Defining the response to treatment

This is an important indicator as to the effectiveness of chemotherapy.

Complete response (CR)

This is the goal when treating patients with visible tumour and is determined by our inability to detect cancer cells after administering chemotherapy to a patient with visible tumour. When evaluating potentially new drugs it is the complete response rate that is the prerequisite for cure. The most important indicator of a CR is the relapse-free survival time after treatment has been discontinued.

Partial response (PR)

A partial response equates to at least a 50% reduction in tumour volume; in some patients this may be sufficient to give improved quality of life.

Stable disease (SD)

In stable disease there is no measurable reduction in tumour size, so it can be difficult to decide if treatment is or is not benefiting the patient.

Other estimates of treatment value include the median response duration and the median survival time. Although the goal is cure, the reality is very different due to the development of drug resistance by tumour cells. The development of resistance depends on a number of factors. Rapidly dividing cells, e.g. high-grade lymphoblastic lymphomas or acute leukaemias, may respond quickly to chemotherapy but will also develop resistance rapidly as well. As the use of drugs that have similar mechanisms of action can lead to rapid drug resistance, good balanced combination protocols focus on utilizing drugs that kill by different mechanisms.

Mechanisms of resistance

Drug resistance is ultimately the cause of treatment failure. A number of mechanisms are involved in the development of drug resistance. A full discussion of this topic is beyond the scope of this book but a number of comprehensive texts are available for those readers interested in pursuing this further (Chu & DeVita 2005, Tannock & Goldenberg 1998).

Intrinsic

Some tumours respond poorly to chemotherapy from the beginning and therefore are rarely considered to be candidates for chemotherapy. In humans, cancers with intrinsic resistance include renal carcinoma and melanomas. In veterinary oncology, intrinsically resistant tumours would include melanomas, soft tissue sarcomas and gastric carcinomas.

Acquired resistance

Initially response to treatment is good, with patients achieving a CR. Eventually, however, a relapse occurs and, when it does, a change in protocol may be required to re-induce a remission. In veterinary medicine, lymphoma – the most common cancer that is treated by chemotherapy – falls into this category.

Anatomical resistance and drug delivery

If the drug cannot reach the tumour because of anatomical considerations, e.g. the blood–brain barrier, then this will lead to treatment failure, even if the tumour would have been intrinsically sensitive to chemotherapy at another anatomical location.

Specific mechanisms of resistance

Specific mechanisms of resistance are seen most frequently with the antimetabolite drugs, e.g. methotrexate (amplification of the dihydrofolate reductase gene).

Cellular transporters

A number of membrane-bound efflux pumps influence the distribution of cytotoxic drugs. The best known of these is P-glycoprotein (P-170) or MDR-1. The natural function of

P-glycoprotein is to protect the body against xenobiotics and is found distributed in the gastrointestinal tract, hepatocytes, biliary tract and renal tubules. Increase in the production of P-glycoprotein promotes efflux of a number of cytotoxics derived from natural products and includes the vinca alkaloids, anthracyclines and actinomycin D. Currently, an assay is available to screen dogs for expression of MDR-1 (Culmsee et al 2004) and this has been linked to increased toxicity to chemotherapy drugs in collies. For those patients testing positive, increased gastrointestinal toxicity is encountered with the above classes of drug and they should be used with caution in these patients.

Other membrane glycoproteins, including multidrug resistance protein (MRP), have also been identified, but as yet stratagems to circumvent these resistance mechanisms are not available.

Genetic mechanisms

Changes in gene expression of such entities as p53 are other mechanisms by which cells can achieve resistance.

It is important to remember that the mechanisms of drug resistance are multifactorial. Therefore, in order to combat drug resistance, a number of strategies will be required.

New developments

Metronomic regimens

These protocols employ standard chemotherapeutic agents, but at lower doses in a continuous schedule instead of large doses given in pulses. The goal behind the metronomic delivery of chemotherapy is to target the blood vessels within a tumour. These blood vessels are continually growing and therefore are susceptible to the effects of chemotherapeutics. Because chemotherapy is ongoing, the toxicity is reduced, as is the ability of damaged cells to repair themselves (Gately & Kerbel 2001).

Development of new agents – anti-angiogenesis

- Matrix metalloproteinase inhibitors
- Agents that target pro-angiogenic factors – vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)
- Agents that inhibit endothelial cells, e.g. angiostatin (Folkman 2005).

This type of treatment should be considered as cytostatic, meaning that a CR may not be the goal and therapy needs to be maintained long term.

Tyrosine kinase inhibitors (PTKI)

This class of new agents holds great promise for the future. Tyrosine kinases are important enzymes in cellular communication and, when activated due to oncogene mutation, can lead to abnormal cellular growth, i.e. neoplasia. PTKIs inhibit the reaction between ATP and substrate protein, preventing phosphorylation of the substrate and resulting in inhibition of downstream signalling (Traxler et al 2001).

Chronic myelogenous leukaemia (CML) in humans is the result of a reciprocal translocation in chromosomes 9 and 22 that leads to the bcr-abl oncogene product. Imatinib mesylate is a PTKI aimed at this gene product that is currently available for the treatment of humans with refractory CML (Cohen et al 2002). This agent also inhibits other oncogene-induced tyrosine kinases (c-*met* and c-*kit*) and therefore may be of value in other neoplasms. Again, this type of therapy is static rather than toxic and so may form part of future treatment strategies. Preliminary results have shown responses in cats with feline vaccine-associated sarcomas (Lachowicz et al 2005) and much interest has been generated in their potential application in the management of canine mast cell tumours due to their expression of c-*kit* (London 2004).

'New' methods of delivering 'old' drugs

Pegylated liposomal encapsulated doxorubicin (Doxil) has a longer plasma elimination half-life, lower plasma clearance and a reduced volume of distribution compared to doxorubicin. The belief is that by encapsulating doxorubicin in liposomes, the accumulation of drug in tumour tissue will be enhanced (Gabizon & Martin 1997). Doxil has been evaluated in a number of canine tumours, including haemangiosarcoma, given both intravenously (Vail et al 1997) and intraperitoneally (Sorenmo et al 2007).

Table 6.8 Weight (kg) to body surface area (BSA; m^2) conversion chart for dogs

kg	m^2	kg	m^2	kg	m^2
2.0	0.160	19.0	0.719	36.0	1.101
3.0	0.210	20.0	0.744	37.0	1.121
4.0	0.255	21.0	0.769	38.0	1.142
5.0	0.295	22.0	0.785	39.0	1.162
6.0	0.333	23.0	0.817	40.0	1.181
7.0	0.370	24.0	0.840	41.0	1.201
8.0	0.404	25.0	0.864	42.0	1.220
9.0	0.437	26.0	0.886	43.0	1.240
10.0	0.469	27.0	0.909	44.0	1.259
11.0	0.500	28.0	0.931	45.0	1.278
12.0	0.529	29.0	0.953	46.0	1.297
13.0	0.553	30.0	0.975	47.0	1.302
14.0	0.581	31.0	0.997	48.0	1.334
15.0	0.608	32.0	1.018	49.0	1.352
16.0	0.641	33.0	1.029	50.0	1.371
17.0	0.668	34.0	1.060		
18.0	0.694	35.0	1.081		

Table 6.9 Weight (kg) to body surface area (BSA; m^2) conversion chart for cats

kg	m^2	kg	m^2	kg	m^2
1.4	0.125	4.4	0.269	7.4	0.380
1.6	0.137	4.6	0.277	7.6	0.387
1.8	0.148	4.8	0.285	7.8	0.393
2.0	0.159	5.0	0.292	8.0	0.400
2.2	0.169	5.2	0.300	8.2	0.407
2.4	0.179	5.4	0.307	8.4	0.413
2.6	0.189	5.6	0.315	8.6	0.420
2.8	0.199	5.8	0.323	8.8	0.426
3.0	0.208	6.0	0.330	9.0	0.433
3.2	0.217	6.2	0.337	9.2	0.439
3.4	0.226	6.4	0.345	9.4	0.445
3.6	0.235	6.6	0.352	9.6	0.452
3.8	0.244	6.8	0.360	9.8	0.458
4.0	0.252	7.0	0.366	10.0	0.464
4.2	0.260	7.2	0.373		

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Principles of radiation oncology

Radiation for the treatment of veterinary patients is a limited but invaluable resource. It has many applications in veterinary medicine and can be used as sole treatment or more commonly in combination with surgery or chemotherapy. It is a localized treatment and therefore has limited application for patients with disseminated tumours.

How does radiation kill cells?

In the energy ranges used in veterinary oncology the major effect is an indirect one due to the production of free radicals. Living cells consist of approximately 85% water, so the major target of ionizing radiation are water molecules resulting in the production of hydroxyl radicals that in turn damage the DNA. The effects of radiation are not specific for cancer cells and rapidly proliferating normal tissues are susceptible to damage and are known as acutely or early-responding tissues. More slowly dividing normal cells (e.g. bone) are affected by radiation but the changes may take months to years to become apparent; such tissues are known as late-responding tissues.

Cell death

Most cells die what is known as a reproductive death and at standard clinical doses the effect of radiation is limited to dividing cells. Clinical effect is dependent on the growth fraction and doubling time of the tumour cells.

Cell death not requiring mitosis can be achieved at high doses when resistant cells become susceptible. A special case is lymphoid tissue that undergoes both mitotic and interphase death at low radiation doses.

The oxygen effect

Hypoxia protects cells from radiation damage; conversely, high oxygen levels fix the free radical damage. Most cells within a tumour are to some degree hypoxic, as a distance of 100 m from a capillary bed results in hypoxia.

Delivery of radiation

Ionizing radiation can be delivered by an external source (teletherapy), by application of radioactive sources interstitially (brachytherapy) or systemically by radioactive isotopes, e.g. iodine-131 (^{131}I).

External beam radiotherapy

Orthovoltage

- Produces x-rays of low to medium energy (150–400 kVp).
- Penetration is low with maximum dose delivered to the skin.
- Increased absorption of radiation in bone relative to soft tissue.
- Not suitable for treating deep-seated tumours.

There are still a few centres worldwide that use orthovoltage machines for veterinary patients but the wider availability of megavoltage machines continues to make these machines obsolete.

Cobalt-60

- First of the megavoltage machines that allowed treatment of deep-seated tumours.
- Skin-sparing effect means the maximum dose of radiation is not delivered to the skin.
- Cheaper to install than a linear accelerator, but has potential radiation considerations due to the presence of a radioactive source.

A few centres worldwide do have cobalt units for the treatment of veterinary patients but newer facilities are installing linear accelerators.

Linear accelerator (Linac)

These megavoltage machines have a number of energy ranges; the most commonly used machines are those with energy of 6 MV (6 million volts) (**Figure 7.1**).

The advantage over orthovoltage machines is the skin-sparing effect. The skin is spared because the maximum dose is delivered at some distance below the skin surface, resulting in fewer side effects to the skin and the ability to treat deep-seated tumours. The point at which maximum dose is delivered (D_{max}) depends on the energy of the machine. The absorption of megavoltage radiation is not dependent on the density of the tissue and so permits an even distribution of radiation throughout all tissues in the field, i.e. bone does not preferentially absorb radiation and therefore reduces the risk of complications involving bone.

Megavoltage radiation results in less scatter and therefore less radiation sickness.

The drawback to installation of a Linac is the cost of the installation, machine and running costs.

Figure 7.1 A 6 MV linear accelerator.

Brachytherapy

- Iridium-192 (^{192}Ir) wires
- Strontium-90 (^{90}Sr)

Brachytherapy is rarely used in veterinary oncology because of the difficulties in using implants in veterinary patients (reviewed by Walker 1997). Isolation wards are required and, depending on the implant, the patient may require isolation for days to weeks. However, ^{192}Ir implants have been used in the treatment of nasal tumours (Thompson et al 1992). Strontium-90 has limited application in the treatment of very small, superficial nasal planum squamous cell carcinoma in the cat or small superficial mast cell tumours in the cat (Turrel et al 2006). Brachytherapy units are commercially available that will undoubtedly find increasing application for veterinary patients.

What are the goals of radiotherapy in the veterinary patient?

Curing the veterinary patient

Radiotherapy as the definitive treatment is rare in veterinary patients and is usually seen as an adjunctive treatment, e.g. in the management of incompletely resected mast cell tumours and soft tissue sarcomas. The most common situation where radiotherapy may be used as the sole treatment with curative intent is in patients with localized lymphoma, e.g. it is the treatment of choice for feline patients with nasal lymphoma (**Figure 7.2A,B**; see Chapter 22).

Adjunctive therapy for incompletely resected tumours

Adjunctive therapy is the most common application of radiotherapy in veterinary medicine. The typical patient has had either a mast cell tumour or a soft tissue sarcoma removed with incomplete margins and radiotherapy is used to clean up the 'dirty' margins when a further surgery is not possible because of anatomical considerations or client preference (**Figure 7.2C**). This means that the tumours are predominantly located on the distal extremities or facial area. See the relevant chapters for a more in-depth discussion.

Neoadjuvant therapy for large inoperable tumours

In cases where a tumour is too large to be surgically excised, or too deeply attached to underlying structures, radiotherapy can be used to shrink the tumour to make it operable (**Figure 7.2D**).

Palliative therapy

Radiotherapy can be used to control pain in patients with inoperable bone tumours (Thrall & LaRue 1995) or in instances of metastasis to bones, e.g. mammary or prostatic tumours. It can be used to relieve physical obstruction by shrinking down tumours to alleviate pain and distress, e.g. metastatic anal sac adenocarcinoma to regional lymph nodes or large inoperable primaries (**Figure 7.3**). In many cases it is the only treatment modality for large inoperable brain tumours and for patients with granulomatous meningoencephalomyelitis (GME) that is non-responsive to medical management.

The majority of patients receiving radiotherapy are treated with megavoltage Linacs and are given a number of treatments over a period of weeks. The principle of fractionated radiation dose depends on a number of considerations that include the principles of radiation biology, the goal of treatment for the veterinary patient (this may be different from the goal in the human patient) and the access, cost, etc. of treatment. However, clients need to be informed of the various options for, and the benefits and risks of, these treatments.

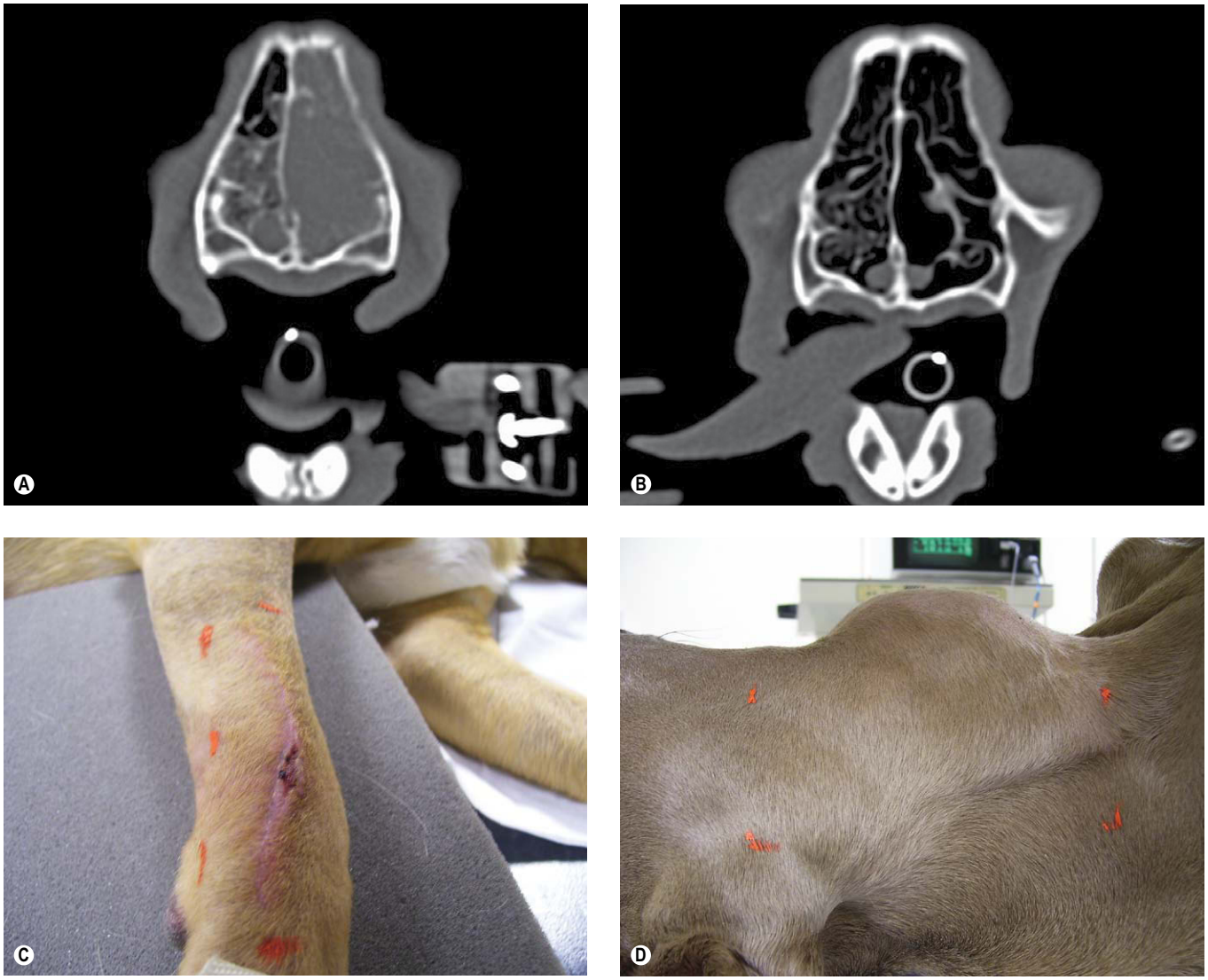

Figure 7.2 CT scans (**A**) before and (**B**) after radiotherapy in a cat with nasal lymphoma. (**C**) Adjuvant radiotherapy on a dog with an incompletely resected soft tissue sarcoma. (**D**) Neoadjuvant radiotherapy on a dog with a haemangiosarcoma on the ventral neck.

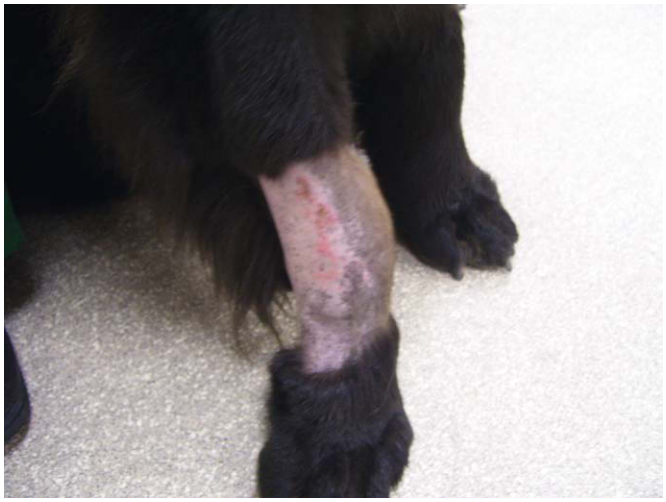

Figure 7.3 Palliative radiotherapy on a large breed dog with osteosarcoma of the distal radius.

Firstly, we should consider the principles of radiobiology that govern our thoughts on why radiation is given in fractions rather than in one large dose.

The 4 'R's' of radiobiology

Not all tumours are equally radio-responsive, and this difference is primarily due to differences in tumour biology, i.e. the heterogeneity of tumours that includes growth fraction, hypoxic fraction, cell kinetics and the rate of cell loss. The principles are therefore designed to promote the death of tumour cells whilst minimizing the consequences to normal cells (Hall 2000).

Repair

Sublethal damage can be repaired. Fractionation allows normal cells to repair, but neoplastic cells do not have sufficient time to repair.

Repopulation

The regeneration of tissues depends on the recruitment of stem cells and this is slower in neoplastic tissue. Fractionated doses allow acutely responding normal tissues to regenerate and repopulate; however, if the treatment time is prolonged, then neoplastic cells will also repopulate.

Redistribution

Cells redistribute through the cell cycle and cells surviving a dose of radiation tend to synchronize in the resistant S phase of the cycle. Redistribution is particularly important in tumours with a low growth fraction.

Reoxygenation

Hypoxic cells are resistant to radiation. Reduction in the number of oxic cells after a cycle results in previously hypoxic cells receiving better oxygen supply and therefore becoming susceptible to radiation.

The question remains as to what is the optimal protocol to minimize damage to normal tissues and to maximize the ability to kill tumour cells. The answer to that question is unknown but over the past 20 years veterinary radiation oncology has made a number of advances along with human radiation oncology in achieving this goal. In human radiation oncology what is known as fine fractionated protocols have been developed that rely on small doses of radiation (200 cGy/treatment) given daily; in some cases multiple doses of radiation will be given the same day. These protocols are designed to maximize delivery of radiation to the tumour and minimize side effects to normal tissue. These protocols are still evolving.

In the 1920s the first veterinary radiotherapy protocols were developed by an Austrian veterinary surgeon, Alois Pommer, and his protocol of a few large fractions given over a short period of time was widely used for many years. This protocol is now known as accelerated hypofractionation. The main reason for developing such a protocol back then was concern about multiple anaesthesias and the cost. Almost 90 years later these protocols are still used and still have some application in veterinary oncology. In many cases, however, fine fractionation protocols are better suited to the overall control of neoplasia; smaller doses per fraction spare the late-responding tissues such as bone and allow larger total doses to be given (see Table 7.1). This was illustrated in one study that examined the late complications of irradiating the pelvic canal in dogs. Dogs that received lower dose/fraction 2.7 Gy instead of 3.3 Gy/fraction had fewer late side effects, in this case colitis, but overall the complication rate was low (Anderson et al 2002).

Fraction size limits total dose and, as can be seen from Tables 7.1 and 7.2, many tumours require a total dose of around 50 Gy. To illustrate how fraction size impacts on normal tissue toxicity, heart failure can be induced by irradiating the whole heart to a total dose of 62–68 Gy using 2 Gy fractions, 60 Gy in 3 Gy fractions and 52 Gy in 4 Gy fractions.

Table 7.1 Comparison of radiotherapy fractionation protocols

Dose/fraction and interval between fractions	Total dose (Gy)
4 9 Gy weekly	36
12 4 Gy MWF	48
16 3 Gy MWF	48
30 2 Gy M–F	60

MWF, Monday, Wednesday and Friday; M–F, Monday to Friday.

Limitations of radiotherapy

As previously discussed, a tissue diagnosis is essential as not all tumours/tissues have equal sensitivity to radiation. Radiotherapy is a local treatment and normal tissue sensitivity limits the dose that can be given (see Table 7.2). In general, haematopoietic tissue is the most radiation sensitive, followed by epithelial and finally mesenchymal tissues. The interested reader is advised to consult a more advanced text for detailed discussion of normal tissue tolerance (Hall 2000).

Side effects from radiotherapy

Complications that can arise from radiotherapy are classified as:

- acute or early
- delayed or late.

Acute

These are seen at the time of treatment and should be handled symptomatically; if severe they may result in treatment delays

Table 7.2 Sensitivity of normal tissues to radiation

Tissue	Sensitivity to ionizing radiation	Injury
Bone marrow (whole body)	++++	Aplasia
Bone marrow	+++	Pancytopenia
Liver	+++	Hepatitis
Lung	+++	Acute respiratory distress syndrome
Kidney	+++	Acute/chronic renal failure
Gastrointestinal tract	++	Ulcer
Brain/spinal cord	++	Infarct
Heart	+	Pancarditis
Skeletal muscle	+	Myositis, fibrosis
Bone	+	Necrosis, osteoporosis

++++, exquisitely sensitive (total dose <3 Gy); +++, sensitive (total dose up to 40 Gy); ++, moderately sensitive (total dose up to 50 Gy); +, relatively resistant (total dose up to 75 Gy).

so early management is essential (Table 7.3). The most commonly encountered acute reaction is moist desquamation and local inflammation (**Figure 7.4**). For the client this can be distressing and the most important aspect of treatment is to stop the dog licking the affected area, which usually means a buster collar, and a lively dog with a buster collar on for a few weeks can be stressful to both client and radiation oncologist.

Providing the acute affects of radiation are handled appropriately, the patient should recover quickly, usually within 2–4 weeks (Hall 2000). Acute early effects are typically seen in rapidly dividing tissues such as epithelium. In some instances healing may become an issue, especially if the radiation burn occurs in a region with a great deal of movement, such as over a joint, e.g. behind the stifle or over the elbow. Occasionally, non-healing wounds may develop. Should healing not occur as expected, the radiation oncologist should be consulted; however, patience and good management usually do pay off.

Table 7.3 Acute (early) side effects of radiotherapy

Tissue	Injury	Treatment
Skin	Moist desquamation alopecia	Buster collar, anti-inflammatory steroids, antibiotics if infected
Oral cavity	Mucositis, halitosis	Antibiotics, usually metronidazole
Nasal cavity	Nasal discharge	Broad spectrum antibiotics
Ocular	Conjunctivitis, keratoconjunctivitis sicca	Eye medication depending on cause
Food pad	Slough, nail loss	Prevent licking – buster collar, antibiotics if necessary
Pelvic canal	Colitis	Antibiotics and anti-inflammatory steroids

Late

Signs of delayed toxicity may have an acute onset, but may not occur until months to years after radiation treatment (Table 7.4). These include leukotrichia, which in itself is not a problem although clients need to be made aware of this before starting treatment (**Figure 7.5**).

The more severe delayed effects obviously depend on the area of treatment. In younger patients treated with radiation for incompletely resected mast cell tumours or soft tissue sar-

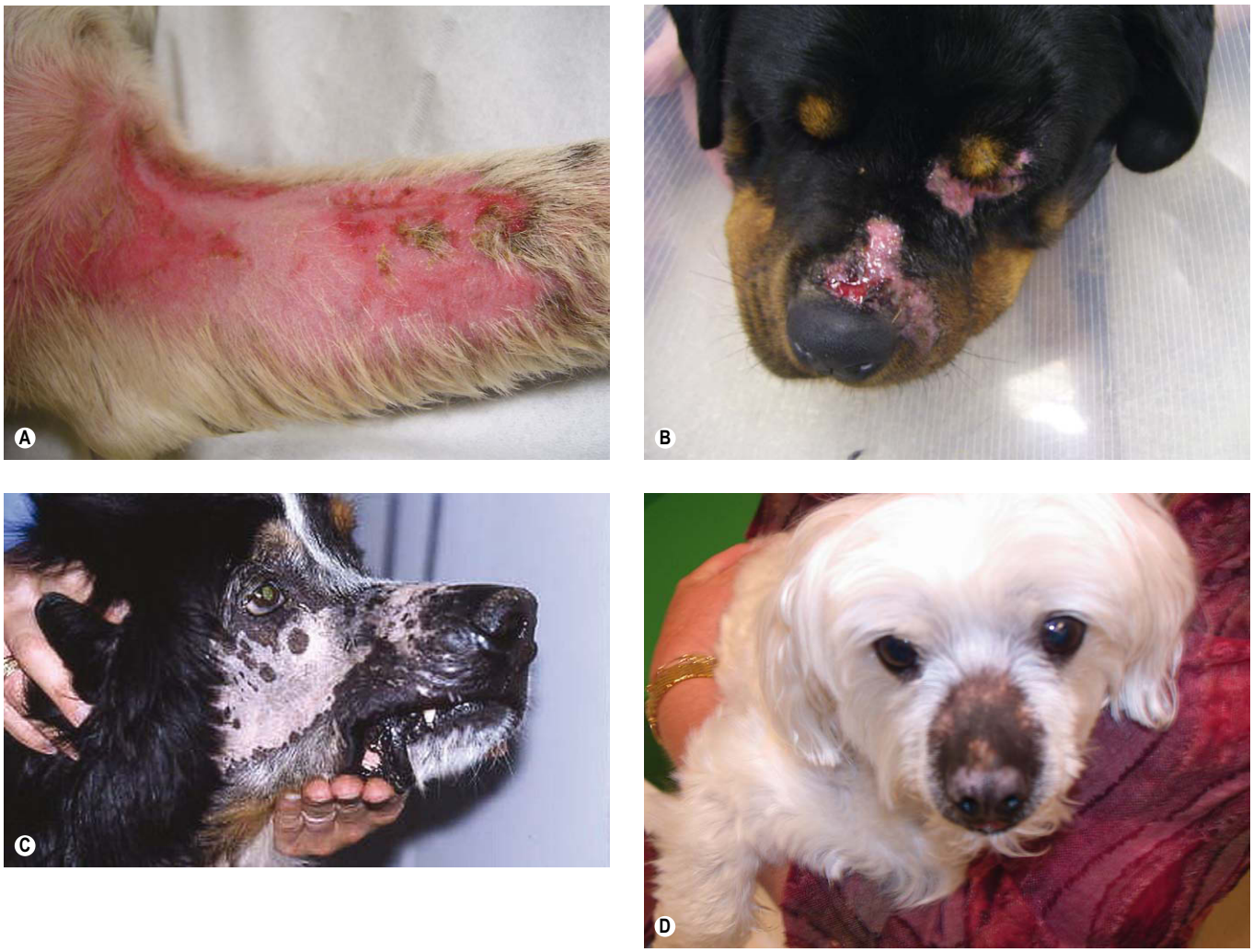

Figure 7.4 Acute effects of radiation. (**A**) Hyperaemia; (**B**) moist desquamation; (**C**) alopecia; (**D**) hyperpigmentation. (Figure 7.4D – Courtesy R Straw.)

Table 7.4 Chronic (delayed) effects of radiation

Tissue	Injury
Skin	Fibrosis, leukotrichia, non-healing ulcer
Oral	Bone necrosis, periodontal disease
Ocular	Keratoconjunctivitis sicca, cataract, retinal damage
Extremity	Neuropathy, contracture
Gastrointestinal tract	Stricture
Brain	Encephalopathy
Spinal cord	Myelopathy
Lung	Pneumonitis
Bone	Fracture, second tumour

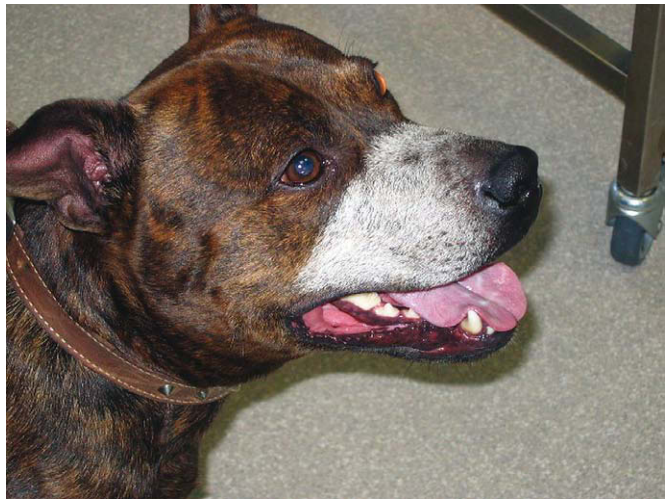

Figure 7.5 Late effects of radiation – leukotrichia.

comas there is the possibility of bone necrosis 5–7 years after treatment that may eventually result in a pathological fracture; even less frequently the development of a second tumour may occur.

How do we treat the veterinary patient?

Firstly, tumour volume must be defined. The treatment volume is always larger than the tumour volume to ensure all neoplastic cells are within the treatment field. If the tumour volume and hence the treatment volume is not accurately determined, then treatment failure due to a geographic miss may occur. Also, it is important to 'spare' as much normal tissue as possible. Other considerations include regional lymph nodes that should be included in the treatment field.

The more accurate the determination of tumour volume, the better the outcome for the patient as regards tumour control. Accuracy also means fewer complications as a consequence of treatment.

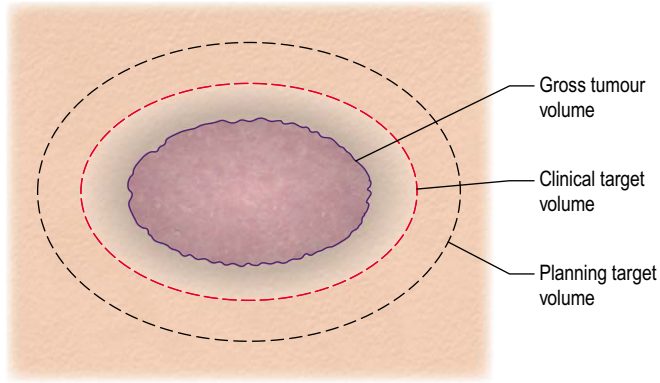

Figure 7.6 Determination of treatment volume.

How do we define tumour/ treatment volume?

Successful radiation treatments depend on an accurate plan. It is important to treat not only visible tumour but also a suitable margin of normal tissue to ensure including subclinical disease within the treatment field (**Figure 7.6**). It is also important to minimize the exposure of normal structures whenever possible. In 1993 the International Committee on Radiation Units and Measurements (ICRU) set up a standard nomenclature to define treatment volume to facilitate dose prescription and reporting of treatment planning, and veterinary radiation oncologists apply the same definitions:

- Gross tumour volume (GTV) is the clinically detectable disease.
- Clinical target volume (CTV) is GTV plus microscopic extension of the tumour.
- Planning target volume (PTV) is GTV + CTV + margin thought necessary to account for any uncertainties in treatment.
- Treated volume (TV) is volume of tissue that will receive the prescribed dose. It must include PTV.
- Irradiated volume (IV) is the volume of tissue given a clinically significant dose.

In many instances the patient is presented with a surgical scar from incomplete resection of a tumour, usually either a mast cell tumour or a soft tissue sarcoma on a distal extremity that is not amenable to further surgery. The surgical scar can be a poor indicator of the actual location of residual disease and accurate surgical and pathology reports are important to provide the best treatment in these patients. The use of hemoclips to identify tumour margins radiographically improves the radiation oncologist's ability to accurately determine tumour volume. The best results in these cases are when the surgeon and radiation oncologist consult and agree on the approach before the initial surgery. Radiographs are also valuable tools to determine tumour volume. Advanced imaging, CT and MRI give the most accurate definition of tumour volume and can be directly linked with computer-associated dosimetry planning (**Figure 7.7**).

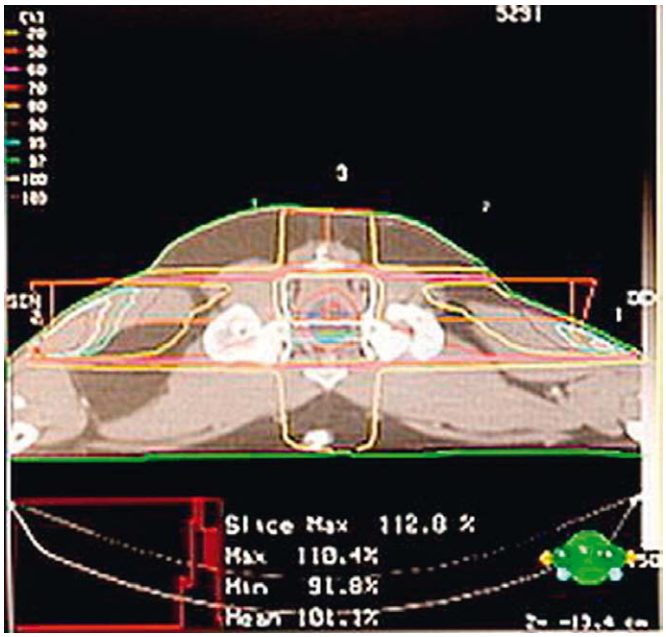

Figure 7.7 CT scan and computer plan.

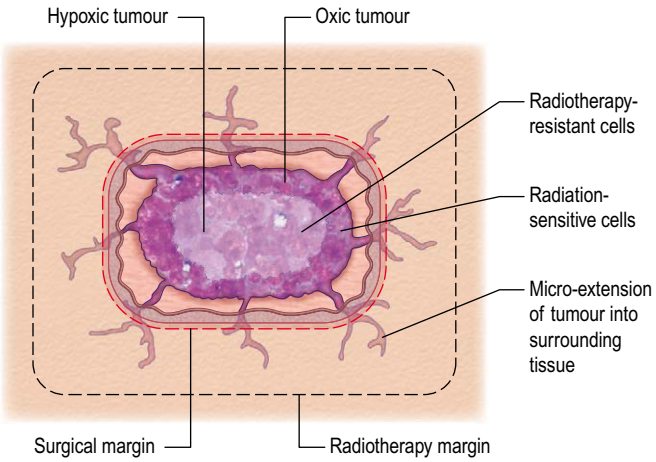

Figure 7.8 Effectiveness of surgery and radiotherapy in tumour management. Hypoxic cells in the centre of the tumour are resistant to radiotherapy. Tumour at the periphery is likely not to be removed by surgery.

How do we ensure reproducibility when treating the veterinary patient?

It is essential that the veterinary patient remain absolutely still during treatment, otherwise the reproducibility of the treatment cannot be guaranteed. This means a general anaesthetic is required. The actual treatment time is very short and therefore the anaesthetic time is only around 10 minutes depending on the complexity of the treatment. To reduce the number of catheters placed for patients undergoing fine fractionated protocols, a vascular access port can be placed (Evans et al 1994).

Bony landmarks assist in the positioning of some patients, and often the treatment field on a distal extremity will be marked with paint to allow accurate and quick realignment on subsequent treatments. The generation of a port film using the radiation generator is used to confirm the treatment field (McEntee & Thrall 1995).

In order to protect normal tissues from radiation, blocks can be used to shield normal structures; however, it is important not to shield the tumour with a block system. Blocks can be custom designed for individual patients, e.g. a brain block for the pituitary and a mantel block for the mediastinum. Multileaf collimators (MLC) attached to the Linac allow conformal therapy that outlines the treatment volume and protects the surrounding normal tissue. Using an MLC allows an increased delivery of radiation to the tumour without increased toxicity to normal tissues.

Maximizing the biological effect of radiotherapy

Cancer management is a multimodality discipline with radiotherapy playing a central role. It is important, therefore, to look at all treatment modalities and determine how they can work together synergistically for the benefit of the cancer patient.

What are the strengths and weaknesses of oncological surgery and radiation, and can we use these factors to the benefit of the patient?

Radiotherapy is most likely to fail at the centre of the tumour due to the protective effect of hypoxia. Surgery often fails at the periphery of the tumour due to residual disease (**Figure 7.8**).

What comes first – surgery or radiotherapy?

Cytoreductive surgery decreases the hypoxic population of cells within a tumour and also results in residual cells being recruited into the growth fraction that will increase their sensitivity to radiation.

Preoperative radiation decreases the size of the tumour to ease resection and can make an inoperable tumour operable because it eliminates the cells at the margins and also decreases the chance of tumour implantation and dissemination from manipulation of the tumour. This particularly applies to mast cell tumours where radiation results in a real reduction in tumour margins; however, it is important to remember that steroids do not have the same effect on the tumour margins.

Intraoperative radiotherapy is used infrequently in veterinary medicine but has application where the surgeon knows the resection is unclean and there is significant concern that tumour may repopulate before standard radiotherapy can be used. A single dose is given and then followed up with conventional external beam radiation.

Postoperative radiotherapy is the most typical application and is used to eliminate residual disease. The limitation of this approach is that the time allowed for healing may result in tumour repopulation. Typically, radiotherapy should start within 10–14 days after surgery, but delays in wound healing or access to facilities may result in delay. High-grade tumours that are more likely to repopulate early should always be treated as soon as wound healing after surgery allows, i.e. 7–10 days.

Table 7.5 Tumours amenable to radiation therapy

Skin tumours	Head and neck	Brain and spinal cord	Thoracic tumours
• Mast cell tumours • Soft tissue sarcomas • Vaccine-induced sarcomas (feline) • Squamous cell carcinomas (feline) • Sweat gland adenocarcinomas • Sebaceous adenocarcinomas **Intrapelvic and rectal tumours** • Rectal/anal carcinomas • Rectal lymphoma • Metastatic lymph nodes	• Melanoma • Squamous cell carcinoma (canine) • Oral fibrosarcoma • Oral lymphoma (including epitheliotrophic) • Salivary gland adenocarcinoma (feline and canine) • Osteosarcoma (palliative) • Plasmacytoma • Nasal tumours • Frontal sinus squamous cell carcinoma • Thyroid carcinomas • Pharyngeal and laryngeal tumours (esp. lymphomas) **Bone tumours** • Pain relief in the management of osteosarcoma • Pain relief for metastatic lesions to bone	• Gliomas • Meningiomas • Granulomatous meningoencephalomyelitis • Lymphoma • Plasmacytoma • Metastatic disease **Urogenital** • Prostatic carcinoma • Mammary carcinoma	• Thymomas • Thymic lymphomas • Metastatic mediastinal lymph nodes • Lung tumours **Round cell tumours** • Lymphomas • Plasmacytomas

Does chemotherapy have a synergistic role in combination with radiation?

Many patients having radiotherapy will concurrently receive chemotherapy targeted at micrometastatic disease. However, that is not the only role for chemotherapy and certain chemotherapeutic agents can act synergistically with radiation to increase cell kill by their different but complementary effects on DNA. The most commonly used agents in this respect are alkylating drugs, platinum compounds and doxorubicin. In humans combinations of cisplatin chemotherapy and radiation in treating patients with head and neck tumours resulted in improved survival times (Jeremic et al 2000).

The 'best' protocol is unknown in terms of time of delivery and dose of the cytotoxic agents, but routinely they are administered before radiation (2 hours) and at a lower dose than in standard protocols to prevent toxicity. The recommended treatment is dependent on tumour type (most commonly bulky sarcomas and carcinomas) and radiation protocol.

The following represent some of the tumours that can be treated with radiation, either as the sole treatment or in combination with surgery:

- mast cell tumours (e.g. Frimberger et al 1997)
- soft tissue sarcomas (e.g. Cronin et al 1998, Kobayashi et al 2002, McKnight et al 2000)
- nasal tumours (e.g. LaDue et al 1999)
- lymphoma (e.g. Elmslie et al 1991)
- brain tumours (e.g. Heidner et al 1991, Turrel et al 1984)
- thyroid tumours (e.g. Théon et al 2000).

(See Table 7.5 for a list of tumours amenable to radiotherapy.)

Detailed discussion and more extensive bibliography of the application of radiotherapy to these tumours will be discussed in the relevant chapters. Non-neoplastic conditions that can be treated with radiation include inflammatory conditions such as granulomatous meningoencephalomyelitis (Munana & Luttgen 1998).

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Other treatment modalities

In addition to surgery, chemotherapy and radiotherapy, other treatment modalities have been evaluated. The majority of these approaches have limited application; some are still in the early phases of evaluation whilst others are no longer recognized as being valuable adjuncts to standard therapies. A brief discussion of these approaches to cancer treatment follows but readers interested in these topics are advised to consult specialist texts for further information.

Other treatment modalities include:

- biological or immunotherapy
- electrochemotherapy (ECT)
- cryosurgery
- photodynamic therapy (PDT)
- hyperthermia
- laser therapy.

Biological or immunotherapy

Harnessing the power of the immune system to kill neoplastic cells has been an area of intense interest and research for a number of decades. The complexity of the immune system is still being unravelled and the networks by which it is regulated means that immunotherapy is still not considered a treatment option for the majority of patients with cancer; when it is, it is seen as part of a multimodality approach rather than as sole treatment.

The immune system consists of a number of effector cells – cytotoxic T cells, natural killer (NK) and lymphokine-activated killer (LAK) cells – that interact with themselves, antibodies and accessory cells (macrophages, dendritic cells) in response to stimulation. Additionally, the properties and behaviour of the tumour can influence the outcome of these immune responses. Tumour characteristics that influence the immune response include the histology, anatomy and magnitude of the tumour, the immunogenicity of tumour cells and their ability to produce immunosuppressive factors or recruit suppressor cells.

Approaches to biological therapy have included:

- non-specific stimulation of the immune system
- specific stimulation of the immune system.

Non-specific stimulation

Older studies evaluated a number of non-specific immunostimulants that included bacillus Calmette–Guérin, *Corynebacterium parvum*, levamisole and acemannan, and finally liposomal-muramyl tripeptide (L-MTP) to which a number of tumours showed some response.

Liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE)

L-MTP-PE is a non-specific activator of monocytes and macrophages. Without the liposomal coat MTP is rapidly removed from circulation so encapsulation allows adequate delivery to target sites and ensures that it remains localized for sufficient time to allow activation of effector cells.

The best-known application of L-MTP-PE in veterinary oncology was its combination with platinol-based chemotherapy in the management of canine osteosarcoma (Kurzman et al 1995, MacEwen et al 1989) and splenic haemangiosarcoma (Vail et al 1995). In all cases treated, L-MTP-PE was used in the adjuvant setting in combination with standard chemotherapy protocols. In one such report the median survival time for dogs treated with L-MTP-PE was 14.6 months compared to 10 months for dogs not receiving L-MTP-PE (Kurzman et al 1995). Unfortunately, in spite of the early promise, limited availability has restricted the use of L-MTP-PE in veterinary oncology.

Specific stimulation

This includes:

- lymphokines and monokines
- adoptive cellular therapy
- antibody therapy
- growth factors
- vaccines.

Lymphokines and monokines

Interferons alpha, beta and gamma (IFN-α, -β, -γ) form a class of small glycoproteins that have a number of biological activities in the body and were initially characterized for their production in response to viral infections.

IFNs have a number of effects on cells, including induction of apoptosis and inhibition of angiogenesis by inhibiting the proliferation of vascular endothelial cells and therefore potentially targeting the vasculature of tumours. IFNs increase the activity of NK cells and IFN-γ can activate cytolytic T lymphocytes. IFN-α has been used in infants with haemangioma and patients with Kaposi's sarcoma. IFN-α also appears to have some activity against human melanoma, particularly in patients with stage II and III disease (Kirkwood et al 2001). Melanoma, as the most immunogenic of all solid tumours in humans, will preferentially lend itself to biological therapy

and is the tumour against which vaccine therapy to stimulate the immune system has yielded the most exciting results (see below).

Human recombinant IFNs are available but as yet their efficacy in canine tumours has not been established. Human IFNs have been used in the management of cats with retroviral infections and in one early study feline leukaemia virus (FeLV)-positive cats given low-dose IFN-α (0.5 U) had increased survival times (500 days) compared to untreated cats (73 days) (Cummins et al 1988). The problem with using xenogeneic recombinant material is the development of neutralizing antibodies and recombinant feline IFN is now commercially available.

Interleukins

Interleukin-2 (IL-2) is a 15 kD glycoprotein secreted by activated helper T lymphocytes and has a number of regulatory functions. When certain populations of lymphocytes are exposed to IL-2 they acquire the capability of killing tumour cells. This activity is described as lymphokine-activated killer (LAK) cell activity. Liposome-encapsulated IL-2 has been used as an inhalant against pulmonary metastases.

Antibodies

The initial promise of using monoclonal antibodies (MAB) directed against tumour-associated antigens has not impacted on the management of veterinary patients. One MAB directed against antigens expressed on canine lymphoma cells (MAB 231) was developed in the early 1990s and became commercially available (Jeglum et al 1987).

Growth factors

Granulocyte–macrophage colony-stimulating factor (GM-CSF) promotes the growth and differentiation of neutrophils and cells of monocyte lineage. Administration of GM-CSF to patients increases the levels of circulating neutrophils, eosinophils, macrophages and lymphocytes. Recombinant human GM-CSF has a number of applications in human oncology, including the management of chemotherapy-induced neutropenia. The immunostimulatory function of GM-CSF is also being explored in vaccine production (see below).

Vaccines

The concept of anti-tumour vaccines is not new but with increasing technology a number of potential anti-tumour vaccines are currently being evaluated. Malignant melanoma is the most immunogenic of all solid tumours and is resistant to chemotherapy, making it an ideal tumour with which to explore the possibilities of developing biological means of attack. These include using autologous or allogeneic tumour cells genetically modified with DNA coding for GM-CSF (Hogge et al 1998). Other cancers under investigation for vaccine development include B-cell lymphoma, again involving genetically modified GM-CSF.

Currently, one melanoma vaccine developed in the USA has a conditional license for the treatment of canine patients (see Chapter 13).

Recently, U'Ren et al (2007) reported on the preliminary results of a vaccine directed against canine haemangiosarcoma cells.

Electrochemotherapy

Electrochemotherapy (ECT) combines the local or systemic administration of a chemotherapeutic agent with the application of electrical pulses to increase the uptake of drug by neoplastic cells. Drugs that have enhanced uptake include bleomycin and cisplatin. Results to date have been anecdotal (Spugini et al 2006, 2008).

Cryosurgery

Cryosurgery is the controlled destruction of unwanted tissue by the application of cold temperatures. Cooling temperature (–20°C) for 1 minute or longer destroys almost all unprotected mammalian cells (Mazur et al 1970, Walter 1970). In recent years it has become less popular because of the superior results and greater access to radiation and lasers.

Advantages

Cryosurgery is relatively safe (avoidance of risks of general anaesthesia) and rapid (Withrow et al 2007). The dimensions of freezing can be controlled with proper technique and equipment (Withrow 1980a) and there is no general systemic reaction. There is lack of haemorrhage (if no incision or ulceration) and minimum postoperative discomfort. Postoperative infection is rare (Fretz & Holmberg 1980). Freezing can be repeated without cumulative effects and can be used on tissue not readily treatable by conventional surgical techniques.

Disadvantages

The disadvantages of cryosurgery include limited indications, post-freezing odour and slough of necrotic tissue which may be severe when large areas are frozen (Krahwinkel 1980). The initial investment is relatively high and liquid nitrogen has a short storage life (Withrow et al 2007). Postoperative oedema may be life-threatening, e.g. oral cavity or pharynx. Some areas may be slow to heal, e.g. bone. Skin and hair may be depigmented (Withrow et al 2007). Scar tissue around areas such as the anus may cause strictures (Liska & Withrow 1978). Run-off cryogen can cause necrosis of normal tissues. Excessive freezing can destroy adjacent tissue whereas inadequate freezing will allow tumour recurrence. It is impossible to know with true certainty if adequate margins of frozen tissue have been achieved around malignant masses. Follow-up to monitor for local tumour recurrence is very important.

Indications

Cutaneous lesions

Cutaneous lesions include localized inflammatory and benign tumours. Treatment does not require a sterile field. Small, superficial, benign cutaneous and perianal tumours may be treated under sedation and local anaesthetic injected under the lesion, particularly if multiple lesions are present (Krahwinkel 1980). However, more extensive disease requires general anaesthesia. Tumours <2.5 cm are considered for cryosurgery. Larger tumours, especially aggressive tumours with life-threatening potential, are better treated surgically when possible (Withrow et al 2007).

- *Ophthalmic*: palpebral tumours, dermoids, distichiasis and melanocytes on corneal surface are all more cryosensitive than adjacent normal tissue (Holmberg 2003).
- *Perianal*: small benign lesions are good candidates. In the management of perianal adenomas, cryosurgery has no advantage regarding rates of recurrence than other treatments (Holmberg 2003).
- *Oral*: small benign lesions are good candidates. Treatment of malignant lesions of the oral cavity with cryosurgery is expected to produce poor local disease control rates. However, cryosurgery may be used as palliative therapy for malignant oral tumours, e.g. geriatric patients where the client is unwilling to consider definitive treatment either by surgery or radiotherapy (Holmberg 2003).

Contraindications

Mast cells lysed by freezing release histamine and heparin locally. Local erythema and slough for the size of tumour may be excessive (Holmberg 2003), and rapid degranulation may induce hypotensive shock (Withrow et al 2007).

Tumours that have major bony involvement do not respond well and should not be treated by cryosurgery (Withrow 1980b) due to low water content of cortical bone and high vascularity of cancellous bone (Holmberg 2003). Freezing cortical bone kills cells and reduces strength by up to 70% (Gage et al 1966), so that spontaneous fracture is a continued risk months after treatment (Holmberg 2003). Liquid nitrogen vaporizes when sprayed directly onto cancellous bone.

Fatalities due to air embolization causing cardiac arrest (cancellous bone to venous sinus to right atrium) have been reported (Harvey 1978). Major blood vessels can be destroyed by necrosis and slough of surrounding tissues. Any large vessels within target tissues should be ligated beyond the limits of freezing to prevent haemorrhage when the eschar is shed (Holmberg 2003).

Photodynamic therapy

Photodynamic therapy (PDT) involves the administration of a substance known as a photosensitizer that, when activated by light of a specific wavelength, shows activity against neoplastic cells. Photosensitizers can be administered by a number of different routes (oral, intravenous, topical) and optimally they are selective for tumours (cells in S phase are the most sensitive). The limitation of PDT is that only superficial lesions can be treated; this is because, with systemic administration of a photosensitizer, the depth of penetration of the light is usually 1–1.5 cm, the actual depth depending on the wavelength. When the photosensitizer is administered topically the depth of penetration is even less (0.5 cm).

How does PDT work?

The photosensitizer converts light energy into chemical energy by interacting with other molecules whilst in an electrochemically active state. Two types of reaction are possible:

- *Type 1*: the excited photosensitizer reacts directly with other substrates to produce free radicals
- *Type II*: the excited photosensitizer transfers energy to molecular oxygen, converting it to singlet oxygen, which then goes on to cause oxidation of cellular macromolecules.

In either Type I or Type II reactions the overall effect is free radical damage leading to cell death. Type II reactions are considered to be the most clinically relevant.

Although destruction of tumour cells occurs directly, the majority of damage is caused to tumour vasculature, resulting in ischaemia and cell death. Inflammatory cells are also recruited to the tumour and assist in tumour destruction (**Figure 8.1**).

Photosensitizers are activated using a light source, typically a laser, that produces a single wavelength and therefore will work only with one photosensitizer. It is the cost of the lasers that significantly restricts the application of PDT in veterinary oncology. Laser light can be delivered through optical fibres of small diameter (~400 nm) making it suitable for treatment of visceral tumours using endoscopy. These small fibres can also be placed directly into tumours for interstitial PDT (e.g. canine prostatic carcinomas).

One important aspect of PDT is that it causes both apoptosis and necrosis within tumours, so tumours that have lost the ability to undergo apoptosis are still susceptible to PDT. Also, the amount of light used for PDT is considerably less than with surgical lasers, meaning that tissues do not undergo local heating and the induction of heat-stress proteins.

The advantages and disadvantages of PDT are outlined in Box 8.1.

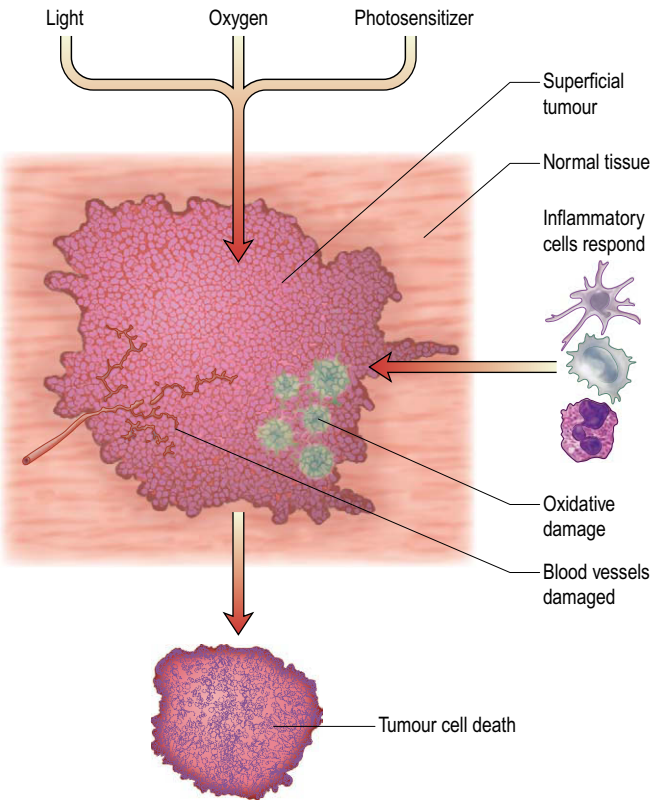

Figure 8.1 Mechanism of tumour cell killing by photodynamic therapy.

Box 8.1

Advantages and disadvantages of photodynamic therapy

Advantages

- One time treatment when compared with other local therapies, e.g. radiotherapy, although treatment may need to be repeated if tumour recurs; however, unlike radiotherapy, normal tissue damage is not a limiting factor
- Safe to surrounding normal tissues
- Well tolerated and fairly non-toxic
- Not cross-resistant with other treatment modalities, e.g. radiation or chemotherapy

Disadvantages

- Applicable to superficial tumours only
- Light sensitization occurs for a period of time
- Repeat treatments required
- Inflammatory reactions frequently encountered
- Availability of treatment

Tumours suitable for treatment with PDT

Squamous cell carcinoma (SCC)

Solar-induced SCC of the nasal planum and pinna is the tumour most commonly treated with PDT in veterinary medicine. A number of studies using different photosensitizers and protocols have been published over the past few years evaluating PDT in the management of SCC and comparing it to the accepted treatment options of surgery or radiotherapy (Hahn et al 1998, Peaston et al 1993).

For cats with early stage (T1–T2) disease, overall tumour control is significantly better than for those patients with large and invasive tumours, and at 1 year tumour control in one study was in the order of 61% (Magne et al 1997). This study demonstrated results similar to radiation therapy. Stell et al (2001) reported a complete response of 85% with topical PDT; however, 7 out of 11 tumours recurred and the median disease-free interval was only 21 weeks. The advantage in this study was that although the median was less than in other studies, no toxicity was encountered in the cats as had been seen with systemic administration of the same photosensitizer. This study showed that, at least for this agent (5-aminolaevulinic acid), the topical route, although causing no side effects, resulted in poorer overall tumour control. Buchholz et al (2007) reported 75% 1-year control using a liposomal formulation of the photosensitizer meta-tetrahydroxyphenylchlorin (m-THPC). No systemic side effects were recorded in patients given the liposomal formulation and mild local side effects were recorded in 15% of patients (erythema and oedema).

SCC in the dog is generally treated with surgery, radiotherapy or a combination of the two treatment modalities. Small tumours may be amenable to PDT (McCaw et al 2000) using pheophorbide-a-hexylether-based PDT. Efficacy similar to segmental mandibulectomy or maxillectomy was demonstrated in this one study.

Canine prostatic carcinoma

Canine prostatic carcinoma has been used as an experimental model in the development of PDT protocols for human prostatic carcinomas (Huang et al 2005), but as yet treatment using PDT has failed to result in long-term control in client-owned dogs.

Other tumours that have been treated with PDT include haemangiopericytoma (McCaw et al 2001) and oesophageal SCC in a dog (Jacobs & Rosen 2000). The wider application of PDT to these and other tumours has not been assessed.

Acute side effects from treatment include erythema and oedema, the treated tumours becoming necrotic within a few days of treatment. Other side effects include inappetence and infection at the injection site.

Photosensitizer evaluation

A number of photosensitizers have been evaluated over the last decade, including haematoporphyrin derivative (HPD) and dihaematoporphyrin ester/ether (photofrin II). Photofrin II is a mixture of chemicals with absorption coefficients in the 600–900 nm wavelength range, wavelengths that penetrate tissue best. The major limitation of these photosensitizers was the extended photosensitization of 1–2 months.

Other photosensitizers that have been evaluated in veterinary medicine include 5-aminolaevulinic acid, meta-tetrahydroxyphenylchlorin, Sn-ethyl etiopurpurin and aluminium phthalocyanine. Studies have not shown any significant toxicity in dogs, but in cats hepatic changes were reported with 5-aminolaevulinic acid (Lucroy et al 1999) and aluminium phthalocyanine (Peaston et al 1993).

Hyperthermia

Hyperthermia has been explored as sole treatment for certain tumours or more commonly as an adjunct to radiation. The delivery of heat to tumours may be via external sources such as microwaves, radiofrequency or ultrasound depositing energy in the tissues using an external applicator. Alternatively, interstitial hyperthermia results from the placement of the source directly in the tissues.

Local current field (LCF) radiofrequency hyperthermia has been applied to solar-induced SCC in the cat. With LCF radiofrequency, electric currents pass between two electrodes and the tumour placed between the electrodes increases resistance to the flow of current, resulting in the dissipation of heat. Tissue is heated to 50°C for 30 seconds, resulting in destruction of tumour tissue and normal tissue up to 2–3 mm from the electrodes.

Non-lethal hyperthermia results in the induction of heat-stress proteins (HSP) that can lead to thermotolerance and resistance to further treatments. The area of most interest in the application of hyperthermia is in the possible synergistic effects of heat and radiation. Hyperthermia tends to kill cells that are hypoxic (therefore radioresistant) and may inhibit repair of radiation-induced damage. Hyperthermia is selective for poorly vascularized tumours that do not dissipate heat easily (also these tumours will be hypoxic) and so the advantage of combining these two treatment modalities is obvious. However, as the best method of delivering hyperthermia and the optimal protocols have not yet been realized, currently hyperthermia in veterinary oncology is experimental rather than clinical (Maguire et al 2001).

Laser therapy

Laser (light amplification by stimulated emission of radiation) surgery offers better haemostasis, less postoperative swelling and decreased postoperative pain compared to sharp scalpel dissection (Lucroy & Bartels 2003). However, there is little published information to support its use as a major treatment modality in veterinary oncology.

Lasers produce intense, coherent (photons travelling in the same direction with minimal divergence), monochromatic (photons of same wavelength) light in visible, infrared or near UV regions of the electromagnetic spectrum:

- *Lasers of the visible spectrum*: argon, krypton, dye-tuned, helium-neon, ruby crystal. The frequency (Hertz = cycles per second) and the wavelength (nanometres = length between successive waves of light) determine light colour.
- *Infrared lasers*: carbon dioxide (CO_2) and Nd:YAG (neodymium:yttrium-aluminium-garnet).
- *Lasers of UV wavelength*: argon fluoride and xenon chloride.

Light must be coherent and monochromatic for energy to be focused for surgery. Photon wavelength is related to their energy density and how they will relate to tissue. Tissue characteristics such as pigmentation, vascularity, thickness and water content all affect the response of the tissues to the particular type of laser surgery.

The thermal effects of laser therapy are photocoagulation (when >50°C, coagulation of proteins and irreversible cell damage) and photovaporization (when >100°C, rapid increase in cell temperature and tissue water evaporation, generation of steam and localized explosion which divides tissue).

Laser surgical procedures can be performed in contact mode or non-contact mode. Non-contact mode increases the surgical area covered by the laser but decreases the power density and vaporization efficiency (Lucroy & Bartels 2003).

Various operational modes (continuous light emission, pulsed or superpulsed) or switching (extremely high powered, very short period) can be used.

Laser surgical procedures can be divided into two broad categories: incision and ablation.

CO_2 laser is strongly absorbed by water, and so there is minimal thermal damage beyond margins, allowing for precise incision. There is superficial tissue vaporization, so the extent of thermal damage is readily apparent at the end of the procedure (Lucroy & Bartels 2003). CO_2 laser will not penetrate water, cannot go through fibreoptics, and can be used for cutting, vaporizing and ablating (Lucroy & Bartels 2003). Shelly (2002) reported the CO_2 laser an effective tool for excising perianal tumours, rectal tumours, performing anal sacculectomies and treating perianal fistulas. The CO_2 laser can also be very effective in ablating limbal tumours with corneal extension (Gilmour 2003).

Nd:YAG laser has poor water and haemoglobin absorption and penetrates 4–6 nm. When used in contract mode they result in a precise incision and good haemostasis, but collateral thermal damage may extend beyond 4–5 mm into surrounding tissue, so is less precise than CO_2 laser. Nd:YAG laser can be carried via fibreoptics (Lucroy & Bartels 2003). Nd:YAG laser photocoagulation may be an effective means of treating limbal melanoma in dogs and cats (Sullivan et al 1996).

Holmium:YAG and erbium:YAG lasers cut bone and cartilage; they are used for joint surgery and disc surgery.

Laser safety

There exists the potential for serious injury to surgeon, staff and patient (Lucroy & Bartels 2003), requiring careful adherence to workplace health and safety regulations. Complications from tissue burns from the primary beam, reflected radiation, inhalational damage, etc. must be avoided.

Required equipment includes protective eyewear, non-reflective instruments and a 'laser in use' sign. Inadvertent treatment of non-target areas should be avoided; use short bursts of treatment and pack off surrounding tissues, especially around the endotracheal tube, or use aluminium foil wrap or a metal endotracheal tube.

Although laser surgery is an attractive technique for the reasons of less morbidity, less pain (due to vaporization of nerve endings), better haemostasis and less postoperative swelling, there are still the concerns of limited availability, workplace health and safety issues and limited applications to veterinary cancer patients.

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Oncological emergencies

Oncological emergencies can be divided into two major categories – tumour related and treatment related.

Tumour-related emergencies (Table 9.1)

Tumour-related emergencies could be due to the primary effect of the tumour on the patient, e.g. a dog with a ruptured splenic mass, or the secondary effects caused by a paraneoplastic syndrome (PNS), e.g. severe hypoglycaemia secondary to an insulinoma. For a more detailed discussion of PNS and tumour-related emergencies, see Chapter 10.

The goal of this section is to outline how patients with underlying neoplastic conditions may present in the emergency situation, but the reader is reminded that for each category there are many non-neoplastic conditions with similar presentations, so full evaluation and assessment of the patient are essential. Also, the reader is directed to individual chapters for more detailed discussion of each tumour type.

Anaemia

Unless the anaemia has resulted from acute blood loss it is rarely an emergency, even though it is a common sequela not only of neoplasia but also of long-term chemotherapy. The various causes of anaemia are discussed in Chapter 10.

Transfusions should be considered in oncological cases when the patient is clinical for the anaemia or when the packed cell volume (PCV) is falling rapidly. A cat with a PCV of 15 that is not weak, tachycardic or very lethargic does not need to be transfused as an emergency. However, this patient does require close monitoring as the situation could change depending on the underlying cause of the anaemia. If the same cat had a PCV <10%, then a blood transfusion is necessary because the oxygen-carrying capacity of the blood is reduced and cardiovascular collapse can occur.

Depending on the cause of anaemia a number of blood components are available for transfusion; however, whenever possible, component therapy rather than whole blood transfusions are indicated (Feldman 2000; see Table 9.2).

Dogs

The DEA blood groups in dogs are well established and currently blood typing cards are available to check the DEA1.1 antigen (the most immunogenic) before a transfusion (Giger 2000). Both the donor and recipient should be typed. The best donors are DEA1.1 negative. DEA1.1 positive blood should only be given to DEA1.1 positive recipients because of the potential of inducing anti-DEA1.1 antibodies in negative dogs transfused with positive blood (Giger et al 1995). The recent report of a new blood type antigen, Dal, identified initially in Dalmatians, may mean that screening against more than DEA1.1 will be necessary (Blais et al 2007). If multiple transfusions are to be given to a particular patient over a period of days it is necessary to crossmatch all future blood after 4 days to prevent a transfusion reaction.

Accurate records of what has been given to a patient should be recorded on their file. For any anaemic patient the best transfusion product is packed red blood cells as less 'foreign' protein is transfused and there is therefore a reduced likelihood of an adverse immune response to minor histocompatibility antigens. Giving the correct blood component rather than whole blood also reduces the potential for fluid overload in normovolaemic patients.

Cats

The AB blood group system is recognized and consists of three types: A, B and AB. In cats the presence of naturally occurring alloantibodies means that giving the wrong blood type to a patient can result in fatal transfusion reactions, even with a first transfusion. Ideally, a crossmatch should be done prior to any blood transfusion (Giger 2000). The typing cards commercially available can distinguish the two major blood groups recognized in cats, A and B. However, in the rare case of a suspected AB cat, the blood should be sent to an outside laboratory for typing. The prevalence of blood types varies geographically and within breeds (Giger et al 1989, Knottenbelt et al 1999).

Breeds with a high incidence of B blood type include British Shorthair (40%) and Cornish/Devon Rex (30%); breeds with no reported B blood type include Siamese and Tonkinese. Weinstein has recently reported on the presence of an additional red cell antigen, Mik (Weinstein et al 2007). In cats, blood components are not as readily available as in dogs so whole blood transfusions are usually given. Finding a B donor cat can be very difficult and in such instances haemoglobin-based oxygen carrier (HBOC) products are available (Muir & Wellman 2003).

When giving a blood transfusion, the volume to be transfused can be calculated as follows:

$$\frac{k \times wt\,(kg) \times (\text{required PCV} - \text{recipient PCV})}{\text{donor PCV}}$$

where k = 90 for dogs and 60 for cats.

Haemoabdomen

This is most commonly seen in dogs with ruptured splenic/liver masses. It is seen far less frequently in cats and may then

Table 9.1 Tumour-related oncological emergencies

Problem	Cause	Tumour	Treatment
Anaemia	Blood loss	Bleeding tumour – haemoabdomen	Blood transfusion
	Immunity mediated	Lymphoma, leukaemia	Steroids ± blood transfusion
Hyperviscosity	Paraproteins	Myeloma, lymphoma	Fluids, cytoreductive chemotherapy
	Hypercellularity	Leukaemia	Fluids, cytoreductive chemotherapy
	Polycythaemia	Renal carcinoma or metastasis to kidney	Fluids, phlebotomy
Disseminated intravascular coagulation	Disruption to normal clotting process	Haemangiosarcoma, inflammatory carcinoma	Treat underlying tumour, plasma transfusion
Hypoglycaemia	Hyperinsulinaemia	Insulinoma, sarcomas, hepatic neoplasia	I.v. dextrose
	Insulin-like growth factor II		
Hypercalcaemia	Increased PTH	Parathyroid tumour/hyperplasia	Aggressive saline diuresis; furosemide if hydrated, steroids if confirmed lymphoid origin
	Increased PTHrP	Carcinomas, lymphomas, sarcomas	
Effusions	Metastatic cancer	Carcinomas, haemangiosarcomas, lymphomas, etc.	Thoracocentesis, pericardial tap, etc. treat underlying cause
	Thoracic duct obstruction		
Fever	Inflammation	Lymphoma, leukaemia	Fluids, antibiotics, anti-inflammatories
	Infection		
Seizures	Primary brain tumour, hypoglycaemia, hyperviscosity	Glioma, meningioma, insulinoma, myeloma, etc.	Stabilize seizures depending on underlying cause
Urinary blockage	Tumour extension into urethra	Sarcoma, carcinoma	Place urinary catheter

PTH, parathormone; PTHrP, parathormone-related peptide.

Table 9.2 Indications for blood products in canine patients

Condition	Component of choice	1st alternative	2nd alternative
Blood loss anaemia (hypovolaemic)	Packed red blood cells and crystalloid or colloid fluids	HBOC	Whole blood
Blood loss (normovolaemic)	Packed red blood cells	HBOC	Whole blood
Anaemia secondary to bone marrow failure	Packed red blood cells	Whole blood	HBOC
Haemolytic anaemia	Packed red blood cells	HBOC	Whole blood
Disseminated intravascular coagulation	Fresh frozen plasma	–	–

HBOC, haemoglobin-based oxygen carrier.

be due to either haemangiosarcoma (HSA) or mast cell tumour (MCT). The clinical presentation is typically acute collapse and on examination the mucous membranes are pale and there is often a palpable fluid wave. It is important to remember that not every haemoabdomen in the dog is due to HSA and 30 to 50% of splenic masses are benign (Chapter 23). In the emergency situation it is important to confirm that the ascitic fluid is in fact blood. A blood-coloured fluid is not necessarily blood! The peripheral PCV and the PCV of the fluid should be checked and coincide before a diagnosis of haemoabdomen can be made.

Significant fluid in the abdomen means that abdominal radiographs may not be helpful so the best diagnostic tool is an abdominal ultrasound. The presence of a haemoabdomen as a result of a bleeding splenic/liver mass and a low or falling PCV necessitates an abdominal exploratory. Many of these patients are in disseminated intravascular coagulation (DIC) so a clotting profile should be obtained. If the patient is significantly anaemic or the PCV is falling, then a blood transfusion may be needed before or during surgery, and blood products should be available after surgery if bleeding continues. In patients with stable PCV >25% but in DIC, fresh frozen plasma should be given instead of whole blood.

Hyperviscosity/polycythaemia

In veterinary medicine, hyperproteinaemia is the most common cause of hyperviscosity, polycythaemia is rare and

hyperviscosity as a result of significant leucocytosis is also uncommon. Patients with hyperviscosity may present with a number of clinical signs, e.g. epistaxis, hyphema, collapse, weakness or seizures. Establishment of a good minimum database is essential. In the case of hyperviscosity due to paraproteins, fluid therapy is indicated, i.e. 0.9% NaCl at high fluid rates. Polycythaemic patients will also respond to high fluid rates as an initial treatment in the emergency situation. If the PCV is extremely high (>70), phlebotomy should be used to lower the PCV to around 60. The reduction in PCV should be gradual. The amount of blood that can be removed is up to 20 ml/kg and the volume should be replaced with 0.9% NaCl. For patients with hyperviscosity due to leucocytosis, the underlying cause needs to be established; however, if it is a consequence of leukaemia, then chemotherapy needs to be implemented (see Chapter 22).

Disseminated intravascular coagulation (DIC)

DIC is a secondary syndrome seen most commonly in dogs. Tumours associated with DIC include HSA, inflammatory mammary carcinoma, thyroid carcinoma or any advanced tumour (DuFort & Matros 2005). In cats, aggressive ventral abdominal HSA and MCT are the most common causes of DIC.

Clinical presentation will vary; however, many patients with neoplasia may be in a state of compensated or chronic DIC, which means that they will have laboratory abnormalities but no clinical signs. Patients in DIC can present with petechiation, haemoabdomen, haematuria, haemarthrosis or thromboembolism. Confirmation of DIC requires a coagulation profile, preferably with D-dimers. Ultimately, treatment depends on treating the underlying cause but stabilization can sometimes be achieved with fresh frozen plasma transfusions.

Hypoglycaemia

Some tumours are a direct cause of hypoglycaemia, e.g. insulinomas. Hypoglycaemia is associated with a number of other tumours including intestinal leiomyomas, etc. (see Chapter 10). Hypoglycaemia directly due to neoplasia is unusual in the cat. In cases where hypoglycaemia is tumour related, the presenting clinical signs are often neurological (neuroglycopenia) caused by the small carbohydrate reserves found in neural tissue and the brain's high glucose requirement. Any seizuring dog should have blood glucose checked as part of the standard work-up. If blood glucose is low, a blood sample should be taken for an insulin level.

In the emergency situation the seizuring hypoglycaemic patient should be given dextrose intravenously, starting with a bolus and then continuing on intravenous 5% dextrose solution. If the patient responds well, feeding every 4 hours may maintain the blood glucose sufficiently to eliminate clinical signs. If the blood glucose does not respond to 5% dextrose, the concentration should be increased incrementally to a maximum of 10%. It is important to remember that for concentrations greater than 5% a central venous catheter is required.

Diagnostics to determine the underlying cause should be implemented as soon as the patient is stable. The other oncological emergency where hypoglycaemia is important is septic shock (see 'Treatment-related emergencies' below).

Hypercalcaemia

Hypercalcaemia can become an oncological emergency when the patient presents with vomiting, severe dehydration and lethargy. Initial treatment is aggressive saline diuresis to rehydrate the patient and only then can furosemide be considered. Establishing and treating the underlying cause are essential in the management of hypercalcaemia. The causes are discussed in Chapter 10.

Fever

Fever is an infrequent paraneoplastic syndrome, but when seen in veterinary patients with neoplasia it is most frequently associated with haemolymphatic tumours. In the untreated patient where infection is unlikely to be the cause, inflammatory cytokines are responsible (see Chapter 10).

A patient with a high fever may present as an oncological emergency because of extreme lethargy. To rule out infection a haematology profile is required and, as in any sick patient, biochemistry and urinalysis with culture should be undertaken prior to starting fluid therapy. For the infected patient, see 'Treatment-related emergencies' below.

Respiratory distress

Respiratory distress may result from a number of causes that include space-occupying lesions within the upper or lower airway, malignant effusions or pneumonia. Pneumonia can result secondary to primary lung tumours or as a consequence of aspiration, e.g. secondary to megaoesophagus seen as a PNS in patients with thymoma.

The patient in respiratory distress may require sedation and oxygen before much in the way of diagnostics can be carried out. The more stressed the patient, the more critical it is to have control of the airway and reduce stress. Localization of the origin of clinical signs to either upper or lower airway facilitates efficient examination and diagnostics. For patients with upper airway obstruction, temporary tracheostomy may be required or 'tubing'. For patients with lower airway problems, good quality thoracic radiographs are required. Effusions should be drained (see below). Space-occupying lesions should be identified and when the patient is stable full diagnostics carried out. Occasionally patients with lung tumours will present with pneumothorax due to rupture of the tumour and placement of a chest drain is required.

Malignant effusions

Malignant effusions can be pleural, pericardial or abdominal. Of these, pericardial and pleural effusions can be emergencies; the emergency abdominal fluid could be a haemoabdomen (see above) or a septic patient with a ruptured gastrointestinal tumour.

For any patient presenting in respiratory distress, thoracic radiographs are essential. The patient may require stabilization in oxygen first. For a patient with pleural effusion, thoracentesis to drain the chest is the first line of treatment. Once all possible fluid has been withdrawn, re-take the radiograph

to reassess the amount of fluid remaining. This is important as sometimes fluid can pocket and require multiple attempts to drain; also a mass previously not seen because of fluid may become visible after thoracentesis. Fluid analysis, including cytology, is required to confirm the type of fluid and therefore the possible underlying cause (see Chapter 4). A patient with persistent haemothorax requires emergency surgery once other potential conditions that may cause bleeding (e.g. rodenticide toxicity, DIC, etc.) have been ruled out.

Patients with pericardial effusions frequently present for collapse or lethargy. Malignant pericardial effusion is most frequently seen in large breed dogs due to HSA; however, idiopathic pericardial effusion can be difficult to distinguish from neoplasia (Chapter 14). On examination, the patient is usually weak and it is difficult to auscultate the heart and peripheral pulse. An ECG will often reveal electrical alternans and the heart on thoracic radiographs will have a rounded silhouette. Ultrasound of the heart will confirm a pericardial effusion and at that point the pericardium should be drained. Fluid should be submitted for analysis and an echocardiogram performed to rule out a tumour in the right atrium.

Seizures

A seizuring patient is always an emergency. In older patients with no previous medical history of seizures, a brain tumour should be high on the list of differentials. Do not forget that other neoplastic processes can also result in seizures, e.g. hypoglycaemia, as can many metabolic problems, so a minimum database should be established in addition to controlling seizures.

In the absence of any other cause of seizuring, an MRI or CT scan is required to confirm the presence of a brain tumour. In patients with suspected intracranial disease, corticosteroids may be necessary to reduce peri-tumoural oedema; however, it is important to remember that the use of steroids may interfere with diagnostics such as CSF analysis for conditions such as lymphoma and granulomatous meningoencephalitis (GME).

Pain

When is pain an emergency? Acute pain from a pathological fracture and spinal pain due to tumour compression are the most common pain-related emergencies. For patients in extreme pain, opioids are indicated. For a full discussion of pain, see Chapter 11.

Urinary blockage

Occasionally patients with neoplasia will present for oliguria/anuria due to tumour blocking the urethra. The major differential is urethral calculi. Signalment can provide a good indication that obstruction is due to neoplasia rather than a calculus. The typical bladder cancer patient is more likely to be middle-aged to older and had a history of haematuria before presentation. Susceptible breeds include West Highland White terriers and Shetland Sheepdogs. Also, a blocked older female is more likely to have neoplasia than calculi.

Initial treatment is to pass a urinary catheter and obtain a minimum database. Signs of post-renal obstruction should be managed with fluid therapy and a diagnostic work-up carried out (see Chapter 17).

Treatment-related emergencies (Table 9.3)

Treatment-related emergencies include:

- chemotherapy-related emergencies
- surgery-related emergencies
- radiotherapy-related emergencies.

Chemotherapy-related emergencies

When discussing oncological emergencies there is overlap between those that can be caused by the tumour itself and those that can result from treatment. However, for the patient undergoing treatment, these situations are most quickly recognized. The veterinary patient on chemotherapy that is unwell requires prompt evaluation by the veterinary professional.

Fever

Cytotoxic drugs can result in myelosuppression leading to infection. The most common clinical presentation of infection is lethargy as a result of fever. Any cancer patient receiving cytotoxics that presents with fever should have their white blood cell count checked. If the neutrophil count is low (<3000), then antibiotic therapy should be started.

The most common sites of infection in immunosuppressed patients are lower urinary tract or respiratory. A urine sample should be submitted for culture and sensitivity before starting antibiotics. It is recommended to hospitalize patients with a temperature of 40 °C for systemic antibiotics and fluid therapy. For patients not on steroids an NSAID should be given.

Once the fever has resolved the patient can be discharged on antibiotics. If the patient is showing signs of septic shock, immediate aggressive treatment is required.

Sepsis

Clinical signs of sepsis include hyperaemic mucous membranes, increased heart rate, poor pulses, hyper- or hypothermia and collapse. Emergency diagnostics should include blood gases, blood glucose, haematology, biochemistry, urinalysis and culture, and chest and abdominal radiographs. For patients on chemotherapy, sepsis is seen most frequently in dogs. It is relatively uncommon in cats, with carboplatin the drug most likely to cause sepsis in the cat.

Shock fluids should be given at 90 ml/kg/hour in dogs and 50 ml/kg/hour in cats; if the blood glucose is low, the patient should be given 50% dextrose i.v. and started on antibiotics. The typical intravenous antibiotic cocktail consists of a penicillin-type drug, a fluoroquinolone and metronidazole.

Table 9.3 Examples of treatment-related oncological emergencies

Chemotherapy	Surgery	Radiation
Fever	Wound dehiscence	Acute: burn
Sepsis	Bleeding	Chronic: pneumonitis
Tumour lysis syndrome	Infection	Chronic: CNS

Shock cocktail

Many septic patients are hypoinsulinaemic and therefore cannot make full use of i.v. dextrose without the help of exogenous insulin. In cases of septic shock the following can be used via a centrally placed catheter.

- Place glucose 3 g/kg, 0.5 mmol KCl/kg and 1 IU regular insulin/kg in 250–500 ml of Hartmann's solution.
- Give one-third over the first hour and the remainder over a period of 8 hours.

Due to the presence of insulin in the cocktail the patient must remain on dextrose.

Sodium bicarbonate should only be given to the septic patient based on blood gas analysis, and alkali treatment should not be given if the patient has a pH of >7.2. The formula is:

$$\text{MEq } HCO_3 \text{ required} = \text{body weight (kg)} \quad 0.3 \quad (HCO_3 \text{ deficit})$$

Give a quarter of the calculated dose slowly i.v. and place the remainder in fluids to be given over 24 hours. Check blood gases every 4 hours.

Tumour lysis syndrome (TLS)

TLS is rarely seen in veterinary medicine; however, when encountered, it is usually in patients with acute leukaemia or late stage lymphoma and occurs within 24–48 hours after induction chemotherapy. The cause of TLS is rapid cell death leading to the release of potassium, phosphate, uric acid and other purine metabolites to such an extent that the kidney is unable to excrete them. Metabolic abnormalities that result from this are hyperkalaemia, hyperphosphataemia, secondary hypocalcaemia and hyperuricaemia (Altman 2001). Dogs do not become hyperuricaemic due to differences in purine metabolism; exceptions to this would be Dalmatians and English Bulldogs because of a lack of the enzyme uricase. Lactic dehydrogenase (LDH) will also be increased.

Clinically, patients present with signs of acute renal failure and metabolic acidosis, and aggressive hydration (0.9% NaCl) is the single most important treatment. If potassium is extremely high (>8), then insulin/dextrose therapy should be implemented in addition to aggressive fluid therapy. Good supportive care and continual assessment are important if the patient is going to recover (Vickery & Thamm 2007).

Surgery-related emergencies

Patients that present as an emergency after surgery usually have experienced some form of wound breakdown, after removal of abdominal or thoracic tumours, or major cytoreductive surgeries, e.g. large resections and reconstructive surgery for tumours such as MCT or soft tissue sarcoma (STS). For patients with wound breakdown after large resections it is important to obtain a culture from the wound before proceeding with surgical closure, antibiotic treatment or management of an open wound.

Radiotherapy-related emergencies

These can be either acute or delayed effects of treatment. Acute is most likely to be burn associated, with the patient extremely uncomfortable and licking the affected area (see Chapter 7). Other side effects that are seen rarely in veterinary medicine and can occur months to years after treatment include pneumonitis (presenting with severe respiratory distress), radiation-induced hepatitis, nephritis, etc. (clinical signs reflected in the affected organ) or CNS signs after radiotherapy for brain or spinal tumours.

A full history and an awareness of the potential for radiotherapy-related problems are important to facilitate the appropriate handling of the patient.

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Paraneoplastic syndromes

The recognition of paraneoplastic syndromes in veterinary patients is important. In humans the prevalence of paraneoplastic syndromes is high. How high the prevalence is in veterinary patients is unknown but it is probably frequent and underestimated.

What are paraneoplastic syndromes and why are they important?

Paraneoplastic syndromes (PNS) result as a consequence of an indirect effect of tumours that produce biologically active substances, either in the form of hormones or their precursors – growth factors, cytokines or interleukins. The immune system may be involved, resulting in autoimmunity, immune complex formation or immunosuppression.

Recognizing paraneoplastic syndromes is important because:

- it may be the first sign of neoplasia, e.g. polyuria/polydipsia (PU/PD), in patients with hypercalcaemia secondary to an anal sac adenocarcinoma; early detection may lead to a better prognosis for the patient
- monitoring a PNS means that the progression, regression or relapse of a tumour can be followed
- the signs of a PNS can sometimes be confused with the direct effects of neoplasia or treatment, e.g. presentations of anaemia in lymphoma
- a PNS in itself may adversely affect prognosis as it may cause other problems, e.g. renal failure in patients with hypercalcaemia
- the presence of a detrimental PNS means that achieving either static disease or a partial response may not be an option for the patient, e.g. a dog with anal sac adenocarcinoma metastatic to the sub-iliac lymph nodes can be kept comfortable with palliative care (chemotherapy or radiotherapy to reduce the size of the lymph nodes, faecal softeners, etc.), providing he is not hypercalcaemic; for the hypercalcaemic patient the inability to attain a complete remission will result in a reduced life span. This is because the persistence of the PNS will not only adversely affect quality of life for the patient, it will also lead to other significant consequences, e.g. renal failure.

The most commonly encountered PNS in veterinary medicine are anaemia, thrombocytopenia and hypercalcaemia (see Tables 10.1 and 10.2 for some common tumours and their associated PNS).

Anaemia

Anaemia is the most commonly encountered PNS (Fox 1995). In many cases, although present, it is not clinically relevant. When dealing with the anaemic patient it is important to establish the underlying cause and type of anaemia.

Anaemia of chronic disease

This is the most common form of anaemia seen in cancer patients. The mechanisms involved include impaired iron use, suppressed erythroid progenitor cell differentiation, insufficient erythropoietin (EPO) production and decreased survival of erythrocytes. It is characterized as mild/moderate, normocytic, normochromic and non-regenerative, with normal bone marrow cellularity and reduced serum iron. Specific treatment is seldom required but in rare instances EPO may be beneficial.

Haemolytic anaemia

Haemolytic anaemia is most often encountered in association with haemolymphatic tumours (see Chapter 22), but has been reported in association with solid tumours (Ogilvie 2000). The mechanism is due to cross-reacting antibodies against cell-membrane antigens or direct interference with the immune system via suppressor T cells leading to premature destruction of erythrocytes. It can be mild, moderate or severe and is characterized as macrocytic, hypochromic and regenerative.

Any patient presenting with immune-mediated haemolytic anaemia (IMHA) warrants investigation to rule out underlying neoplasia. It can be life-threatening and may require intervention with blood products (packed red blood cells, whole blood or blood substitutes, e.g. oxyglobin; see Chapter 9).

Microangiopathic haemolytic anaemia (MAHA)

This form of anaemia is most commonly seen with haemangiosarcoma (HSA) but can be seen with any microvascular tumour and is due to fragmentation of erythrocytes producing schistocytes. Schistocyte production is the result of intravascular shearing due to the presence of fibrin strands from chronic disseminated intravascular coagulation (DIC) or abnormal tumour vasculature. MAHA can be mild to moderate and may require intervention with blood products.

Blood loss anaemia

Any bleeding tumour can cause blood loss anaemia, e.g. primary gastrointestinal tumours, splenic, renal and hepatic

Table 10.1 Common tumours and haematological paraneoplastic syndromes

Paraneoplastic syndrome	Tumour
Anaemia	Lymphoma, leukaemia, multiple myeloma, haemangiosarcoma, intestinal carcinoma, etc.
Thrombocytopenia	Lymphoma, leukaemia, multiple myeloma, haemangiosarcoma, etc.
Pancytopenia	Leukaemia, lymphoma, Sertoli cell tumour, granulosa cell tumour
Eosinophilia	Mast cell tumours, lymphoma, sarcomas, bladder carcinoma
Disseminated intravascular coagulation	Haemangiosarcoma, inflammatory carcinoma, thyroid carcinoma, lymphoma, leukaemia, any advanced cancer
Polycythaemia	Renal carcinoma/lymphoma
Leucocytosis	Lymphoma, haemangiosarcoma

Table 10.2 Tumours and non-haematological paraneoplastic syndromes

Paraneoplastic syndrome	Tumour
Hypercalcaemia	Lymphoma, leukaemia, multiple myeloma, squamous cell carcinoma, anal sac adenocarcinoma, histiocytic disease, metastatic carcinomas
Hypoglycaemia	Insulinoma, leiomyomas/sarcomas, hepatic carcinomas, haemangiosarcomas
Fever	Lymphoma, leukaemia, solid tumours, etc.
Cachexia	Lymphoma, leukaemia, any advanced neoplasm
Hyperviscosity	Multiple myeloma, lymphoma, leukaemia
Neuromuscular	Thymoma, lymphoma, insulinoma, pancreatic carcinoma, prostatic carcinoma, etc.
Hypertrophic osteopathy	Osteosarcoma, metastatic carcinoma
Skin	Mast cell tumours, pheochromocytomas, carcinoids, haemangiosarcoma, renal cystadenocarcinomas
Hyperhistaminaemia	Mast cell tumours
Renal	Lymphoma, multiple myeloma, anal sac adenocarcinoma, any advanced tumour

tumours. It is also seen with paraneoplastic gastroduodenal ulceration caused by, for example, gastrinomas and mast cell tumours. The mechanism depends on the underlying tumour. The characteristics of the anaemia depend on chronicity as it can start off regenerative and with, for example, a slowly bleeding intestinal tumour, become non-regenerative, microcytic and hypochromic.

Thrombocytopenia

This is the most common haemostatic problem in dogs with cancer, and is seen in up to 30% of dogs with solid tumours and 50% of dogs with lymphoma (Grindem et al 1994, Madewell et al 1980). In cats, feline leukaemia virus (FeLV) and myeloproliferative diseases are the major neoplasms to result in thrombocytopenia and account for 20% of cases (Jordan et al 1993).

Mechanisms include immune-mediated (idiopathic thrombocytopenic purpura, ITP) due to the formation of antiplatelet antibodies or cross-reactivity of platelet antigens and tumour antigens (lymphoma).

Microangiopathy can cause fragmentation of platelets and chronic DIC will reduce platelet numbers (HSA) due to increased platelet consumption. Spontaneous bleeding is expected with a platelet count of $<20 \times 10^9$/l, although bleeding can occur at platelet counts of 50×10^9/l following surgery or trauma.

In patients with thrombocytopenia a coagulation profile is indicated, if possible to include D-dimers to assess the presence of fibrin degradation products (FDPs). Treatment depends upon treating the underlying neoplasm.

Pancytopenia

Pancytopenias are associated with leukaemia and, for solid tumours, most often with Sertoli cell tumours and granulosa cell tumours. In the latter instances the mechanism of pancytopenia is oestrogen-induced production of myelopoiesis inhibitory factor by thymic stromal cells, leading to the inhibition of granulocyte/macrophage progenitor cell growth. In many cases the effect can be long term (Teske 1986). Pancytopenias due to leukaemia are the result of 'crowding out' of normal cells.

Leucocytosis

Leucocytosis in veterinary patients not associated with infection or leukaemia is rare and when seen does not in itself result in clinical signs. It is usually a mature neutrophilia and has been reported with lymphoma, rectal carcinoma, pulmonary carcinoma and metastatic fibrosarcoma. Production of colony-stimulating factors by the tumour is thought to be responsible for the leucocytosis (Sharkey et al 1996).

Hypereosinophilia

This is rarely seen as a consequence of neoplasia. It has been reported in a cat with T-cell lymphoma (Barrs et al 2002) and bladder carcinoma (Sellon et al 1992), and even more rarely in the dog (Couto 1984). It is most often seen in patients with disseminated mast cell tumours and appears to be a response to the production of interleukin (IL)-2 and IL-5 (Gaschen & Teske 2005).

Disseminated intravascular coagulation (DIC)

Greater than 83% of dogs with advanced malignancies have abnormal coagulation tests; although abnormalities are present they are not always clinically relevant.

Mechanisms by which tumours induce DIC are complex and involve the production of coagulation-activating substances by the tumour, e.g. tissue thromboplastin, tumour necrosis factor (TNF), etc. DIC-related bleeding diathesis is most common with HSA, inflammatory mammary carcinomas and thyroid adenocarcinoma.

The clinical signs of DIC can vary depending upon whether or not bleeding or thrombosis is dominant. Clinical signs, laboratory abnormalities, treatment and prognosis in DIC are outlined in Box 10.1.

There are many causes of DIC that are not neoplastic, e.g. heat stroke, sepsis, snake bites; however, if a patient has documented DIC for which there is no known cause, the primary differential would be HSA.

Hypercalcaemia

Hypercalcaemia is a common paraneoplastic syndrome that is most frequently associated with canine lymphoma, often T-cell lymphoma (20% of lymphoma patients) and multiple myeloma (10–15%). The most common site for lymphoma in dogs with paraneoplastic hypercalcaemia is the cranial mediastinum, followed by the bone marrow (see Chapter 22).

Other neoplasms associated with hypercalcaemia include anal sac adenocarcinoma and squamous cell carcinoma; however, any neoplasm may cause a paraneoplastic hypercalcaemia. The hypercalcaemia of malignancy is seen less frequently in cats. Parathyroid tumours or parathyroid hyperplasia will result in hypercalcaemia and should be included in the differential for patients with hypercalcaemia.

Patients with hypercalcaemia may present with symptoms of PU/PD, nausea/vomiting, constipation and disorientation.

It is important when measuring serum calcium to remember that the most common cause of elevated calcium is laboratory error; therefore, before going on a 'cancer hunt', repeat the blood test to ensure its accuracy. When measuring total calcium this needs to done in relationship to serum albumin. It is more accurate to measure ionized calcium that does not require taking into account protein levels:

$$\frac{\text{Corrected calcium (mmol/l)}}{\text{Measured calcium (mmol/l)} - (\text{albumin (g/l)}/40) + 0.875}$$

The mechanism depends on the underlying cause. For a patient with primary hyperparathyroidism, excess production of parathyroid hormone is responsible for the hypercalcaemia; this can be confirmed by checking the level of parathyroid hormone in circulation.

Common mechanisms of paraneoplastic hypercalcaemia

- Focal bone destruction (osteolytic) by the tumour (e.g. extensive bone metastases with multiple myeloma).
- Humoral paraneoplastic syndrome due to the ectopic production of parathormone (PTH) or parathormone-related peptide (PTHrP) by the tumour.

Focal bone destruction

This is mediated by paracrine factors secreted by tumour cells infiltrating bone. These are cytokines and growth factors that increase bone resorption by directly stimulating osteoclasts or by interaction with osteoblasts which then upregulate osteoclast-activating factors.

Humoral hypercalcaemia of malignancy (PTHrP)

This involves factors produced by a tumour that affects bone resorption and/or tubular calcium reabsorption. The most common factor is PTHrP. In humans, PTHrP is detected in ~80% of patients with hypercalcaemia and it can be accurately measured in veterinary patients. In hypercalcaemic patients with lymphoma, PTHrP is usually elevated but the levels have been reported as lower than in other malignancies (e.g. anal sac adenocarcinomas); this would imply that other humoral factors are involved in hypercalcaemia including α-hydroxylase, vitamin D and calcitriol (Kruger et al 1996).

Pathogenesis is multifactorial as PTHrP (or ectopic PTH) can act on target cells in bone, kidney and intestines (**Figure 10.1**).

- *Bone*: stimulates bone resorption and thereby mobilizes calcium.
- *Kidney/intestines*: increases renal tubular calcium resorption, inhibits phosphate (PO_4) resorption and

Box 10.1

Clinical signs, laboratory abnormalities, treatment and prognosis in DIC

Clinical signs

- Petechiae/ecchymosis
- Mucosal bleeding
- Haemorrhage/bleeding into body cavities

Laboratory abnormalities

- Increased activated partial thromboplastin time (APTT)
- Increased one-stage prothrombin time (OSPT)
- Decreased fibrinogen
- Positive fibrin degradation products/D-dimers
- Thrombocytopenia
- Increased activated clotting time (ACT)

Treatment

- Treat the underlying cause
- Fresh frozen plasma (FFP), if available
- Heparin, fragmin (low-molecular weight heparin)
- Fluid support ± blood transfusions
- Other supportive care for the critically ill patient

Prognosis

- Depends on underlying neoplasm and response to treatment

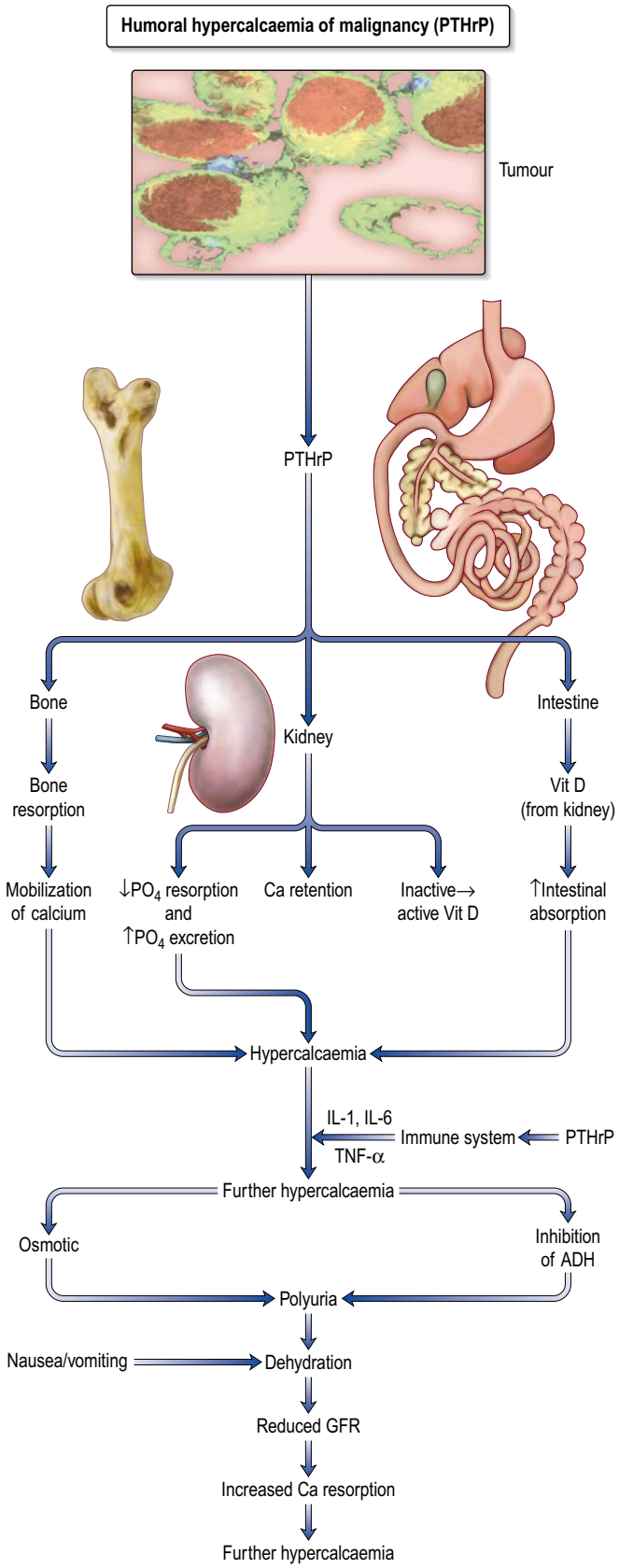

Figure 10.1 Flow chart illustrating the effects of parathormone-related peptide (PTHrP) on calcium metabolism. ADH, antidiuretic hormone; GFR, glomerular filtration rate; IL, interleukin; TNF, tumour necrosis factor.

increases PO_4 excretion, and converts inactive vitamin D to active vitamin D, resulting in hypercalcaemia.

- PTHrP affects paracrine factors including IL-1, IL-6 and TNF-α, resulting in further hypercalcaemia.
- Hypercalcaemia induces osmotic diuresis and inhibits ADH; this results in polyuria. Polyuria plus nausea/vomiting lead to dehydration, reduced glomerular filtration rate (GFR), increased calcium resorption and worsening hypercalcaemia (see **Figure 10.1**).

Humoral hypercalcaemia is associated with carcinomas and sarcomas; focal bone destruction is associated with skeletal metastases and multiple myeloma.

Treatment of hypercalcaemia

This is a medical emergency, as persistent hypercalcemia will result in renal failure, gastritis and reduced quality of life for the patient (Kruger et al 1996).

1. Identify the underlying cause.
2. Fluid therapy (0.9% NaCl) will result in a mild decrease in serum calcium levels, but will not preclude continued effects of PTHrP or ectopic PTH on target cells. Fluids expand the intravascular volume and when the patient is fully hydrated furosemide can be used in conjunction with NaCl to enhance calcium excretion by increasing delivery to, and blocking transport of, calcium and sodium from the loop of Henle.
3. Prednisolone is effective in reducing hypercalcaemia caused by lymphoid tumours but will not significantly improve the calcium levels of patients with solid tumours. Care should also be taken to ensure that the use of prednisolone does not interfere with a final diagnosis.
4. Bisphosphonates inhibit both normal and pathological bone resorption via direct or indirect effects on osteoclasts and are most effective against hypercalcaemia associated with multiple myeloma and solid tumours with skeletal metastases. They are less effective in the therapy of patients with humoral hypercalcaemia of malignancy because they have no effect on tubular calcium reabsorption mediated by factors such as PTHrP.
5. Calcitonin inhibits osteoclast-mediated bone resorption while promoting urinary calcium and sodium excretion. It is used only in the acute setting as it requires frequent administration and the occurrence of tachyphylaxis within a few days.

Hypoglycaemia

The most common cause of this PNS is insulinoma due to hyperinsulinaemia. There are, however, a number of extrapancreatic tumours that can cause hypoglycaemia, e.g. HSA, hepatoma, hepatocellular carcinoma, leiomyosarcoma (Leifer et al 1985).

Proposed mechanisms of extrapancreatic tumour hypoglycaemia

The most common mechanism is the production of insulin-like growth factor II (IGF-II). This results in increased utiliza-

tion of glucose, which has an effect on the patient similar to insulin itself (Gaschen & Teske 2005). Other mechanisms are thought to include:

- increased consumption of glucose by the tumour – thought to occur with hepatic tumours
- increased glucose utilization as a result of ectopic insulin production, increased numbers of insulin receptors, etc.
- tumour production of suppressive factor that inhibits glucagon release or inhibits glycogenolysis
- destruction of sufficient liver by neoplasia to result in decreased glucose production.

Treatment of paraneoplastic hypoglycaemia

1. Remove the underlying cause.
2. Symptomatic treatment with dextrose-containing fluids. Patients may require up to 10% dextrose to maintain blood glucose levels; however, levels do not necessarily have to be normal, as such patients have adapted to a low blood glucose. Dextrose concentrations 5% require the placement of a jugular catheter.
3. Prednisolone can be used to increase gluconeogenesis and decrease peripheral tissue glucose utilization.

Hyperhistaminaemia

This is seen as a consequence of mast cell degranulation resulting in the release of vasoactive substances, typically histamine and heparin (see Chapter 19). Handling mast cell tumours can be sufficient to release these mediators. Typically, local effects are seen, including oedema, erythema and pruritus. Systemic signs are those of anaphylaxis and can be severe. Steroids and antihistamines should be given for local effects.

The effects of hyperhistaminaemia on the gastrointestinal tract are also important (Ishiguro et al 2003). Binding of histamine to H_2 receptors in the stomach results in excessive acid production that can lead to ulceration. Haematemesis or melaena is seen in extreme cases. H_2 receptor antagonists (e.g. ranitidine) are indicated.

Cancer cachexia

The mechanism of cancer cachexia is complex and in humans there is no consistent relationship between cachexia and duration of clinical illness, clinical stage, tumour location or histology. However, a loss in body weight of >6% is associated with decreased survival times (Howard & Senior 1999).

Cancer cachexia results from a combination of tumour and host factors. Pro-cachectic factors include TNF-α, IL-1, IL-6 and interferon gamma (IFN-γ). Cancer is often associated with anorexia that may be the result of chronic nausea, altered taste perception, early satiety, etc. Inappetence, vomiting and diarrhoea also contribute to cachexia, as do renal and intestinal losses of protein. Abnormal substrate metabolism can precede tumour detection (Daly & Thorosian 1993).

The preferred substrate for tumour cells is glucose that is metabolized via glycolysis. This is an inefficient use of nutrients leading to increased lactate levels. Only two molecules of ATP are produced via glycolysis and all the energy that would have been produced via the tricarboxylic acid (TCA) cycle is lost. Additionally, the body must expend energy to metabolize the lactate, which also results in net loss of energy.

In addition to alterations in carbohydrate metabolism, protein and lipid metabolism are also disturbed (see Chapter 12).

Successful management of the underlying tumour should result in an improvement in the ability of the patient to gain weight.

Fever

Causes of fever include infection and inflammation.

The white blood count is the major criterion in determining the cause of fever, i.e. the presence or absence of neutropenia. In patients with low neutrophil counts infection is primarily responsible for fever (in humans two-thirds). In patients with normal neutrophil counts, only about 20% of humans have infection as the underlying cause of fever.

Cancer cells can produce cytokines that cause fever. In veterinary medicine lymphoma is often associated with fever as a PNS.

Endogenous pyrogens

Interleukin-1 (IL-1)

IL-1 will increase circulating neutrophils and cortisol, and is involved in the acute phase response.

Mature neutrophilia is often seen in cats with intestinal lymphoma and this is probably due to the production of colony-stimulating factors by the tumour cells. Neutrophil count can be used as a subjective indicator of response to treatment.

Tumour necrosis factor-alpha and -beta (TNF-α and -β)

TNF also causes fever, but does not use the same receptors as IL-1. It may induce IL-1.

Other cytokines include IL-6 and interferon.

Treatment of fever

1. Determine the cause of the fever.
2. If infection is confirmed, then antibiotics should be started; if infection is ruled out, then NSAIDs are indicated to inhibit cyclooxygenase and reduce prostaglandin E2 (PGE_2) synthesis.
3. Corticosteroids are also antipyretic; they inhibit PGE_2 synthesis and block transcription of mRNA for pyrogenic cytokines.

Polycythaemia

This is an uncommon PNS but is seen most frequently with renal tumours, either primary or secondary. It is seen rarely with hepatic tumours.

The mechanism involves increased production of EPO in response to hypoxia caused by tumour compression, or ectopic production of EPO. The end result is the clinical signs of hyperviscosity (see Chapter 9).

Hyperviscosity syndrome

Hyperviscosity can be seen as a result of a number of neoplastic conditions. In veterinary medicine it is most commonly associated with multiple myeloma, other dysproteinaemias, polycythaemia and hyperleucocytic acute or chronic leukaemias.

Hyperviscosity syndrome can present as bleeding diatheses – ecchymoses, petechiae, epistaxis, gingival bleeding, melaena, retinal haemorrhages, etc. The cause of bleeding is multifactorial and includes paraproteins acting as coagulation factor inhibitors that can bind to coagulation proteins giving actual deficiencies. Monoclonal proteins can coat platelets that then function abnormally in haemostasis.

Neuromuscular disorders

Generally, neuromuscular disorders as PNS are uncommon; however, it is probable that in veterinary medicine they are underestimated as electromyography is required to investigate 'weakness'. PNS affects the peripheral nervous system more frequently than the central nervous system. Localized or generalized peripheral neuropathies have been reported in dogs with lymphoma, myelomonocytic leukaemia, insulinoma, prostatic and pancreatic carcinoma. Neuromyopathies have been reported most frequently in patients with thymoma, but also in patients with bronchogenic carcinoma, lymphoma, bile duct carcinoma and intestinal carcinoma.

There are a number of proposed mechanisms depending on the underlying neoplasm; these include hormone production, neurotoxins, cytokines and nutrient deficiencies. Autoimmunity affecting the neuromuscular system can be seen due to the presence of specific autoantibodies, e.g. myasthenia gravis due to autoantibodies directed against the acetylcholinesterase receptor (ACh) seen in patients with thymomas.

Skeletal disorders

Hypertrophic osteopathy (HO) is the most commonly seen PNS and is found in patients with pulmonary metastases from primary osteosarcomas; however, it can be seen with other neoplasms secondary to the lung (**Figure 10.2**). The exact cause is unknown but it is thought that vasoactive substances or neurological stimulation lead to increased blood flow, resulting in proliferation of bone and connective tissue. It has been reported that it can be reversed by vagotomy or intercostal neurectomy and therefore stimulation of afferent vagal fibres or parietal pleura may result in efferent stimulation resulting in HO.

Dermatological PNS

There are a number of dermatological manifestations of neoplasia – purpura, flushing, erythema, hyperpigmentation and acanthosis nigricans are a few examples. Flushing is associated with pheochromocytomas, carcinoids and mast cell tumours. In German Shepherds hyperplastic collagenous nodules can appear 1 year prior to renal disease in dogs with renal cystadenomas and nodular dermatofibrosis.

Superficial necrolytic dermatitis (SND) or hepatocutaneous syndrome is rare but has been reported in patients with glucagon-producing pancreatic tumours. Removal of the tumour has been reported to result in resolution of SND (Bond et al 1995).

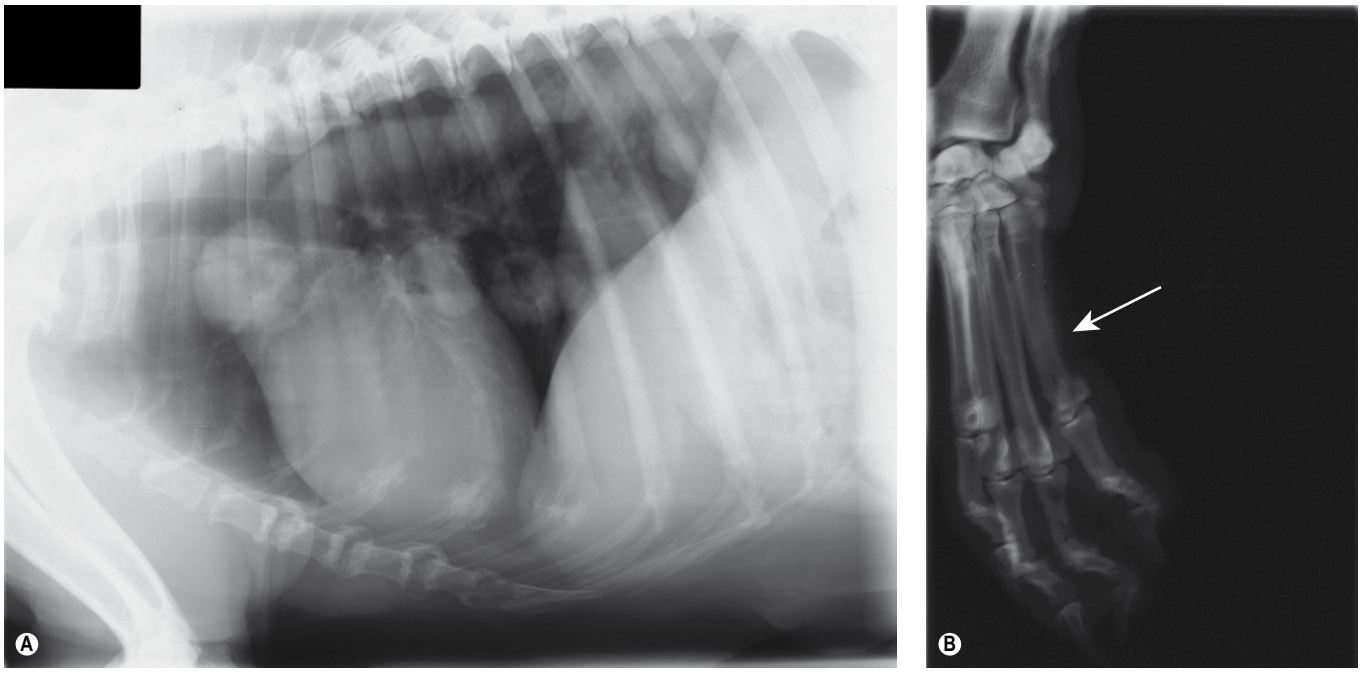

Figure 10.2 Hypertrophic osteopathy in the author's (SN) 14-year-old Labrador retriever. Pulmonary metastases are present, no primary was found.

Renal

Neoplasia can result in secondary renal disease for a number of reasons. Hypercalcaemia, immune complex deposition, and production of amyloid and paraproteins can all have a detrimental effect on renal function. For example, glomerulonephritis (GN) has been reported in ~30% of dogs with local mast cell tumours and around 70% of dogs with mastocytosis. The incidence of GN secondary to neoplasia in veterinary patients is probably significantly underestimated. Deposition of paraproteins in the collecting tubules in patients with multiple myeloma will eventually lead to renal failure.

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Cancer pain

Defining pain in the veterinary patient

The concept of pain is very important to the client, and in many instances one of the first questions on which they will want reassurance is: 'Is (s)he in pain, because I do not want him/her to suffer?'. The 'him or her' in question is usually a very bouncy Golden Retriever that you are having difficulty in examining because (s)he is so lively! However, this does not mean that your very lively patient may not be experiencing pain.

How do we define pain in the veterinary cancer patient and how important is it?

One definition of pain is the unpleasant sensory and emotional experience associated with actual or potential tissue damage (Merskey & Bogduck 1994). There is considerable potential for tissue disruption, pain and suffering with the effects of cancer and with cancer treatment. For example, significant surgical pain may result from wide resections, the creation of large deficits and use of reconstructive techniques. Chronic, insidious, debilitating, continuous dull pain may also result from the effect of cancer on the body. Effective pain management is a vital part of the prolongation of good quality of life, and part of the ethical treatment of our patients (Lascelles & Main 2002).

To understand how to manage pain in our patients it is necessary to understand the different types of pain, the neural pathways involved, what activates these pathways and the clinical signs that indicate pain.

Assessment of pain

Assessment of pain in veterinary patients can be difficult. Animals may not show you they are in pain, and behavioural patterns are a guide only. For example, just because a dog eats, wants a pat and wags its tail does not mean it is not in pain. It is important to recognize that animals instinctively hide pain around people and other animals.

In many cases the presence of pain is subjective and based on behavioural changes that may be subtle and not apparent in the consulting room, but may have caused your client some concern – for example, vocalization, biting/aggression when an area is touched, restlessness, decreased activity, trembling, social withdrawal, changes in eating/drinking/sleeping/elimination patterns, changes in facial expression, biting/licking/guarding or not using a body part.

Objective assessments of pain such as heart and respiration rate, temperature, mucous membrane colour, blood cortisol and adrenaline levels, blood pressure and other physiological responses can also be a guide to pain levels in animals. However, these can be influenced by other factors such as stress, excitement and anxiety and are not always accurate (Conzemius et al 1994, 1997).

Firstly, it is important to address the degree and type of pain that an individual is experiencing.

Degree of pain

- *Mild*: may not significantly change patterns of behaviour and may go unnoticed both by the client and the veterinary professional.
- *Moderate*: will often result in some degree of altered behaviour and the patient will benefit from analgesics.
- *Severe*: requires immediate intervention with analgesics.

Surgical pain

Surgical pain warrants a special mention. All surgery causes pain unless it is treated! It is the responsibility of the surgeon to ensure that all patients are provided with adequate analgesia. This needs to be planned, pre-empted and well thought out. An effective surgical analgesic protocol begins with the premedication and ends when the animal no longer needs it.

The acute pain associated with cancer surgery should not be underestimated. Aggressive resections such as limb amputation and limb-sparing techniques, maxillectomy/mandibulectomy, chest wall resection, nasal planectomy, skin reconstruction techniques, etc. cause considerable tissue damage. Postoperative pain may need to be addressed for up to several weeks.

Acute or chronic pain

Chronic pain is debilitating but because the patient comes to terms with it, it may not be obvious to the veterinary professional, whereas the pain associated with trauma is acute, severe and apparent.

The effects of cancer on the body may also cause chronic pain, which may be insidious/subtle in onset and may be overlooked by the client or veterinarian. Consider the complex pain of a patient with appendicular osteosarcoma. We know that the pain associated with bone tumours is part somatic and part neuropathic, resulting in chronic pain that may only be visualized in the patient by intermittent lameness

(moderate); however, if the dog falls and fractures the leg he will experience acute, severe pain.

Three phases of pain have been proposed by Cervero & Laird (1991).

- *Phase 1*: acute phase, with correspondingly short-lived response in the central nervous system.
- *Phase 2*: prolonged painful stimulation then leads to inflammation and continued discharge of peripheral nociceptors, with subsequent excitability of dorsal horn neurons. Sensitization may occur at either the peripheral (primary hyperalgesia) and/or the central level (central sensitization).
- *Phase 3*: peripheral nerve damage may lead to spontaneous discharge, which modifies (amplifies) the behaviour of dorsal horn neurons (secondary hyperalgesia), and allows peripheral nerves not normally associated with pain to access the ascending pain system and thereby evoke pain.

When a normally non-painful stimulus, even the slightest touch, causes severe pain due to central sensitization, the pain evoked is termed allodynia ('wind-up pain') (Brooks & Tracey 2005). Allodynia is usually due to previous inadequate or lack of pain treatment. The simultaneous use of multiple classes of analgesic drugs is often needed to reverse allodynia. These drugs are gradually withdrawn (the analgesic reverse pyramid approach) (Lascelles 2003).

Classification of pain (Lumb & Jones 1973)

Somatic pain

Somatic pain results in a dull or aching pain that is localized and comes from the stimulation of nociceptors present in cutaneous or deep tissues. Examples of somatic pain include metastatic bone pain and postsurgical incisional pain.

Visceral pain

Nociceptors are activated by infiltration, compression, extension or stretching of viscera. The pain is poorly localized and creates a deep, squeezing, pressure-like sensation. When acute it can be associated with autonomic dysfunction resulting in nausea, vomiting, etc. It is also often referred to cutaneous sites. The kappa-opioid receptors are involved in modulating visceral pain.

Neuropathic pain

Neuropathic pain is a consequence of injury to the central or peripheral nervous system and may result from tumour compression or infiltration of peripheral nerves or spinal cord. Injury to nerves caused by surgery, radiotherapy or chemotherapy can also result in neuropathic pain. Neuropathic pain can be severe.

Complex pain

Complex pain results from stimulation of more than one pathway – for example, bone pain is probably mixed pain involving both somatic and neuropathic pain sensations.

The neurotransmission of pain

(See **Figure 11.1** for an illustration of the neural pathways associated with pain.)

Analgesia is induced by the interruption of nociception (the pathway from pain stimulus to the central perception of pain). A multimodal approach using agents that work at different parts of the pain pathway gives added benefits (see Table 11.1).

Nociception pathway (Practical Pain Management 1988)

Transduction

This is the conversion of physical energy (noxious stimulus, e.g. mechanical, thermal, chemical) into electrical activity (a neuronal action potential) at the peripheral nociceptor (free nerve ending) (Wall 1989). Prostaglandins, bradykinin, leukotrienes and substance P released from damaged cells can directly stimulate nerve endings and can increase sensitivity to subsequent noxious stimuli and other components of the 'inflammatory soup' (Fields 1987).

Transmission

This is the movement of nerve impulses through afferent peripheral and central nervous systems.

- *Peripheral nervous system*: fast transmission through myelinated Aδ fibres (sharp mechanical stimuli) and slow through unmyelinated C fibres (dull, throbbing, longer-lasting pain) (Raja et al 1999).
- *Central nervous system*: pain impulse travels via peripheral nerves to dorsal horn of spinal cord (Basbaum & Jessell 2000). Pain processing (including hyperalgesia and allodynia) occurs in the dorsal horn. Pain-related

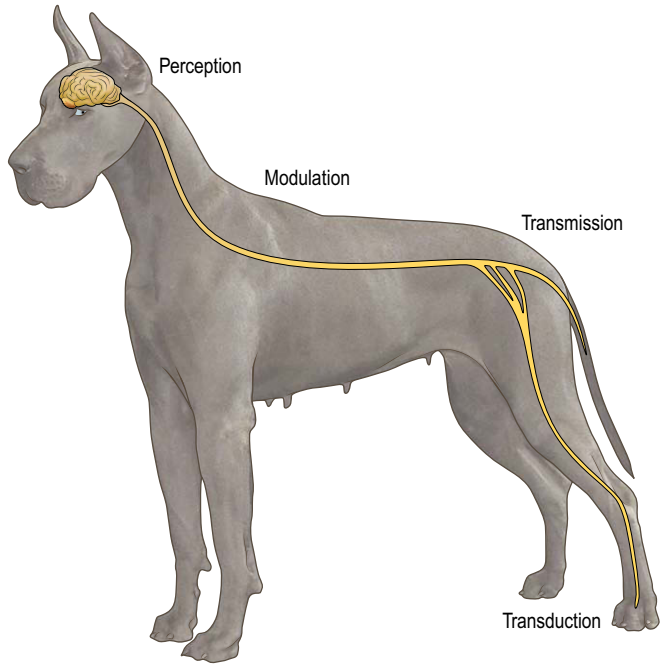

Figure 11.1 The pain pathway.

Table 11.1 Classes of drugs that influence the nociception pathway

Nociception pathway	Drug class	Effect on pathway
Transduction	Opioids, NSAIDs, local anaesthetics	Inhibit peripheral sensitization of nociceptors
Transmission	Local anaesthetics, α_2 agonists	At site/nerves targeting site or spinal canal May interrupt transmission All inhibit impulse conduction
Modulation	Opioids, local anaesthetics, α_2 agonists, tricyclic antidepressants, cholinesterase inhibitors, NMDA antagonists, NSAIDs	Inhibit central sensitization of nociceptors
Perception	Opioids, benzodiazepines, α_2 agonists General anaesthesia	May block perception of pain Blocks perception of pain

(With permission from the Pfizer.)

information then ascends in the contralateral spinothalamic tract (and also direct connections to the medulla and brain stem via the spinoreticular and spinomesencephalic tracts, and to the hypothalamus via the spinohypothalamic tract) to the higher centres in the brain (Brooks & Tracey 2005).

Modulation

Modulation of the pain response occurs through endogenous analgesic systems that modify nociceptive transmission in the spinal column. The 'gate theory' is that the signal sent to the brain is the summation of excitatory and inhibitory impulses (Melzack & Wall 1965). Central sensitization of modulation can be due to the growth of nerve endings under the influence of chemical mediators that fire on their own without peripheral input (McMahon et al 1993). Thus the brain and spinal cord can not only modulate but also create pain perception (Brooks & Tracey 2005).

Perception

Perception is the integration of information in the cerebral cortex, allowing the conscious subjective and emotional experience of pain (Brooks & Tracey 2005).

A number of classes of drugs are available to the veterinary surgeon to interrupt the nociception pathway to provide analgesia (see Table 11.1 and 'Classes of drugs' below).

Rationale for the treatment of pain

Pain is deleterious to the wellbeing of any patient and veterinary professionals have a responsibility to provide appropriate analgesia for their patients.

Why is pain deleterious? (Hellyer & Fails 2003)

The deleterious effects of pain on the body are significant and include:

- increased neuroendocrine response, resulting in increased catecholamines, increased cortisol, increased glucagon and decreased anabolic hormones
- a negative nitrogen balance (catabolism)
- increased medullary stimulation, leading to increased sympathetic tone, increased cardiac workload (increased cardiac output and heart rate), increased respiratory rate and increased vascular resistance
- derangement of autonomic control of abdominal viscera, resulting in ileus and urinary dysfunction
- pulmonary dysfunction
- muscle fatigue.

What we see as a result of these physiological effects is distress and ultimately exhaustion, with the end result of prolonged convalescence and increased morbidity and mortality.

What are the aims of pain management? (Fleming 2001)

The ultimate goal of pain management is to make the patient as free of pain as possible. Practically, this means addressing the emotional and physiological aspects of pain by:

- decreasing nociception (block sensory input, modulate nociception signals)
- decreasing the central perception of pain
- decreasing fear and stress
- decreasing disability due to pain by mobilizing and motivating
- maintaining a comfortable environment and encouraging early interaction.

Guidelines for the rational use of analgesics in the management of cancer pain (Foley 2005)

1. Start with a specific drug for a specific type of pain.
2. Know the pharmacology of the drug.
3. Know the duration of the analgesic effect.
4. Administer analgesic as appropriate depending on (3).
5. If necessary, combine drugs to provide additive analgesia, e.g. narcotic plus non-narcotic.
6. Anticipate side effects/complications.

Therapeutic approach to pain management in the surgical patient (Hellyer & Fails 2003)

The best rule of thumb to use is: 'If it would hurt you, it would hurt them too!'

1. Pain is easier to prevent than treat.
2. The worst way to treat pain is by 'as needed analgesia'.
3. If it would hurt you, it would hurt them. If in doubt, provide analgesia.

4. Opioids are the most effective analgesics.
5. Combination/multimodal analgesia may increase analgesic effects while decreasing the dose and side effects, e.g. synergistic/additive effects of opioids, α_2 agonists, NSAIDs, local or regional anaesthetics, NMDA antagonists, sedatives.
6. Give analgesia prior to surgery.
7. The ideal recovery from surgical or non-surgical anaesthesia should be a smooth transition from anaesthesia to comfortable sleep. Sedatives and tranquilizers may decrease postoperative anxiety. Panic and distress increase the sensation of pain.
8. Do not stop treatment abruptly.
9. Complete pain relief may not always be possible, but a reasonable comfort level allowing quality interaction between client and patient is almost always achievable.
10. Short-term, acute, surgically induced pain: remember that opioids are the best analgesics known! Use them! Combine drugs for synergistic effects by blocking pain at different stages of neurotransmission.

Staging in the management of perioperative pain

The following is an example of an approach to managing perioperative pain. There are three stages to consider: preoperative, surgical and postoperative.

Before surgery

1. Pre-anaesthetic medication: combine sedative and opioid. This has additive/synergistic effects and reduces dose and side effects of each and also the amount of induction agent needed, e.g. acepromazine and methadone/pethidine/morphine/buprenorphine, diazepam and ketamine. Acepromazine 0.02–0.05 mg/kg. Pethidine 1–2 mg/kg s.c. only. Morphine and methadone 0.2–0.5 mg/kg in dogs and 0.1–0.2 mg/kg in cats (morphine s.c. only in cats). Buprenorphine 10 µg/kg q 6–8–12 hours (cumulative).
2. Consider adding a small dose of ketamine (e.g. 1 mg/kg) to the premedication.
3. Add an NSAID to premedication provided there is no evidence of renal or liver dysfunction, no platelet problems and the patient is well hydrated (intraoperative intravenous fluid support and fluid load prior to surgery if needed) with normal blood pressure.
4. Transdermal fentanyl patches. Patches must be in place for 12–24 hours before they become effective, and the duration of effect is 3–4 days. The hair should be shaved closely and cleaned with water (the oil layer is needed for absorption), and the patch covered. Patch size:
   - Dogs and cats <10 kg: 25 µg/hr
   - Dogs 10–20 kg: 50 µg/hr
   - Dogs 20–30 kg: 75 µg/hr
   - Dogs >30 kg: 100 µg/hr.

   Fentanyl patches provide very good pre-emptive analgesia, although additional analgesia may be required. Transdermal buprenorphine patches are also available.
5. Regional analgesia can be beneficial in many patients depending on the planned surgery, e.g. epidurals, intercostal nerve blocks, brachial plexus nerve blocks, infiltration of local anaesthetic into tissue prior to surgery. Epidural: use preservative-free morphine 0.1 mg/kg and make up to total dose with 0.5% bupivacaine at 0.1–0.3 ml/kg.

During surgery

It is important to maintain the level of analgesia.

1. Top-ups of opioids as needed, e.g. pethidine (not intravenous!), fentanyl (only effective for ~20 minutes), methadone or morphine.
2. In many patients an MLK constant rate infusion (CRI) can provide continuous analgesia that can be maintained at reduced doses into the postoperative period. (MLK = morphine 0.2–0.4 mg/kg/hr, lidocaine 1–2 mg/kg/hr and ketamine 1–2 mg/kg/hr; see Box 11.1 for how to set up an MLK CRI.) When setting up an MLK or ketamine infusion, consider the other drugs already given to the patient, e.g. in epidurals, etc.
3. Regional blocks, e.g. brachial plexus, intercostal nerve blocks, local infiltration, splash blocks (e.g. bupivacaine, lidocaine). Bupivacaine is cardiotoxic and must not be administered intravenously. For local infiltration, 2 mg/kg maximum dose every 4 hours, effective in about 20 minutes, and effect lasts 4–6 hours. Lidocaine, 1–2 mg/kg, is effective in a few minutes, but effect lasts only 1–2 hours; cats are more sensitive to toxicity.

Immediate postoperative pain management

It is important to keep the patient as comfortable as possible. Depending on the surgery and the drugs already used, the options for postoperative pain management will vary.

1. Continue opioid CRI or intermittent boluses (pre-empted to prevent pain, not to treat pain once already painful).

Box 11.1

How to set up a MLK constant rate infusion (CRI)

Preparation of infusion

- Remove 33.3 ml of 0.9% NaCl from a 250 ml bag of normal saline.
- Add 25 ml of 2% lidocaine, 5 ml of 100 mg/ml ketamine and 3.33 ml of 15 mg/ml morphine (Lukasik 2006).

Pre-administration

- Prior to commencing the MLK CRI, patients are loaded with lidocaine 2 mg/kg i.v., ketamine 1 mg/kg i.v. and morphine 0.2 mg/kg slowly i.v.
- The initial rate of the CRI is 1 ml/kg/hr.

Post-administration

- If appropriate analgesia is not achieved within 30–45 minutes (or sooner), give increased doses in increments of 3 ml/kg/hr until effective.
- If still not achieving appropriate analgesia, consider additional opioids, local anaesthetic blocks, epidural, etc.

2. Use an MLK CRI (see above). Patients with stable cardiorespiratory function requiring additional analgesia or mild sedation may benefit from the addition of medetomidine (Domitor) at 0.001 mg/kg/hr.
3. Morphine or fentanyl CRIs are excellent for postoperative analgesia, provided the animal is monitored closely. Fentanyl can be given at 2 µg/kg in premedication, intraoperatively at a loading dose of 5 µg/kg, followed by an infusion of 6 µg/kg/hr and boluses of 1–2 µg/kg throughout. Because the patient must be ventilated, MLK or ketamine CRI may be easier in the recovery situation. Fentanyl and methadone are less likely to cause histamine release (important with mast cell tumours) than morphine and pethidine.
4. Continue injectable NSAIDs.
5. Top-up regional analgesia, e.g. epidural catheter.

In addition to the use of drugs, allow the patient to sleep in a quiet, warm and clean environment. Sleep is the great healer and should be facilitated.

Pain management prior to discharge

Once the patient is eating and drinking, then move to oral medication as soon as possible in anticipation of going home.

1. Oral codeine or morphine: dogs 0.3–3 mg/kg every 8–12 hours, cats 0.1–1 mg/kg every 12 hours. Doses may need to be increased above the initial dose range to keep patients comfortable. Unwanted side effects may include sedation, constipation and nausea.
2. Buprenorphine: in the cat oral mucosal absorption is almost complete, but dogs have almost no absorption by this route. Initial dosing in cats is 0.005–0.02 mg/kg under the tongue or along the gingiva.
3. Continue oral NSAIDs.
4. Transdermal fentanyl and buprenorphine patches: remember these are controlled substances and must be dispensed and disposed of appropriately.
5. Top-up regional analgesia, e.g. epidural catheter.
6. Tramadol (Ultram) has a weak, poorly understood mu opioid receptor binding and weakly inhibits the reuptake of noradrenaline (norepinephrine) and serotonin (Lukasik 2006). This is inadequate for moderate to severe pain, but useful for mild pain and in combination with NSAIDs for moderate pain. Analgesic doses in dogs and cats may be closer to 5–8 mg/kg p.o. every 8 hours rather than the lower doses (2 mg/kg) initially recommended (Lukasik 2006); however, at higher doses the degree of sedation can be high, requiring dose reduction.
7. Take care with combining opioids, e.g. patches, CRIs, oral solutions, etc., because all have additive effects. Opioid therapeutic and side effects are dose dependent.

Chronic cancer pain

If acute pain were better controlled, chronic pain may not develop (Hellyer & Fails 2003).

Understated clinical signs such as inappetence, malaise and behaviour changes can indicate chronic pain. This is a real quality of life issue and is as relevant for the animal as obvious, sharp, acute pain. This kind of gradual dwindling of vitality, insidious and subtle, is sure to be under-recognized and under-treated by veterinarians, purely because of the difficulty in detecting subtle changes in behaviour and demeanour when the animal is masking its pain. It is more reasonable to assume that a client who knows their pet well would identify these kinds of changes. The veterinarian should listen carefully to a client's concerns that their pet is in pain, and their descriptions of their pet's behaviour in the home environment. This can often be more indicative of true pain status than behaviour exhibited in the consultation room.

NSAIDs are commonly used for long-term analgesia in cancer patients. Long-term use should be cautionary with known potential toxicity in dogs and cats. Ensure serum biochemistry and urinalysis are assessed prior to and regularly during chronic NSAID use. Other oral analgesic drugs such as codeine, morphine, tramadol, buprenorphine (cats), amantadine, etc. can be added.

Radiation may be used as palliative therapy, particularly for bone pain. Other palliative procedures may be considered such as surgery for ulcerated mammary tumours, amputation for appendicular osteosarcoma, etc.

Summary

In summary, pain can be prevented or successfully managed. If in any doubt it is better to give analgesia than withhold it. Our patients deserve carefully planned analgesic protocols in the acute and perioperative settings, as well as during and after radiation therapy and chemotherapy and in the palliative care arena. If we are unable to provide pain relief, then the plan must be reviewed, ultimately switching gears and considering quality death in the face of being unable to provide quality life.

Classes of drugs

Opioids

- Most effective analgesics known.
- Bind reversibly with receptors (mu, kappa, sigma, delta, epsilon) in the brain and spinal cord and peripheral nervous system:
  - Pure agonists (morphine, pethidine, fentanyl, methadone): can be administered continuously, and therapeutic and side effects are additive. Good for any pain, but especially strong pain, e.g. fractures, bone pain. There is no 'ceiling effect'.
  - Antagonists–agonists (buprenorphine, butorphanol): often adequate for less small soft-tissue surgeries, but insufficient analgesia for fractures/bone pain and more extensive soft tissue surgeries! Have a ceiling effect.
  - Opioids are anxiolytic when combined with low-dose sedation (e.g. acepromazine) = neuroleptanalgesia.
  - Naloxone is a pure antagonist and must be available when administering opioids.

- Side effects include vomiting, dysphoria, euphoria, excitement, respiratory and cardiovascular depression, histamine release, urine retention and ileus.

Alpha-2 (α_2) adrenergic agonists

- Antinociceptive system uses noradrenaline (norepinephrine) as a chemical messenger.
- Can be combined with opioids.
- Potent analgesic and cardiorespiratory depressant.
- Especially useful for visceral pain.
- Most commonly used member of this class is medetomidine.
- Effects are reversed by atipamezole.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- First-line drugs in veterinary medicine.
- Inhibit cyclooxygenase and prostaglandin production (proinflammatory mediators).
- NSAIDs are generally well tolerated.
- Side effects include gastrointestinal, renal, hepatic and antiplatelet. All have some toxic potential. Cox-2 inhibitors have less gastrointestinal toxicity and antiplatelet effects. Cats are more sensitive to toxicity than dogs and at this time meloxicam is the only NSAID licensed for cats.
- Not to be used concurrently with corticosteroids or other NSAIDs.
- Individual responses to NSAIDs can vary; may need to change dose or change the NSAID.
- Most commonly used orally for chronic pain management.
- Examples include carpofen, meloxicam, firocoxib, etolodac, deracoxib, aspirin, ketoprofen, etc.

Local anaesthetics

- Stabilize the membranes of excitable tissues and inhibit transmission of nerve impulses.
- Selectively bind to sodium channels so that no influx or action potential is achieved.
- Inhibit the modulatory nociceptive processing with central administration.
- Examples include lidocaine and bupivacaine.
- Topical creams and the lidocaine patch (Lidoderm) may be beneficial for wounds and ulcerations.
- Lidocaine can be given as a CRI via a surgically placed catheter at a dose of 2 mg/kg/hr in a volume flow rate of 2–5 ml/hr.

N-methyl D-aspartate (NMDA) receptor antagonists

- Activation of NMDA receptors causes the spinal cord neuron to become more responsive to all of its inputs, resulting in central sensitization (Dickenson 1995). NMDA receptor antagonists can suppress this central sensitization, and so are useful for allodynia (wind-up pain) (Dickenson 2002).
- Co-administration of an NMDA receptor antagonist with an opioid may prevent tolerance to opioid analgesia. These drugs can also be used in conjunction with acepromazine or α_2 agonists. CRIs, either alone or in MLK infusions, give good postoperative analgesia.
- Examples include ketamine, tiletamine and amantadine at 3–5 mg/kg every 24 hours.

Selective serotonin reuptake inhibitors (SSRIs)

- SSRIs increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin available to bind to the postsynaptic receptor.
- They are used in humans for the treatment of depression, anxiety disorders and some personality disorders. They may be beneficial as adjuncts in chronic pain patients, e.g. fluoxetine (Prozac).
- Dose: dogs 0.5–1.5 mg/kg p.o. every 24 hours; cats 0.5–1 mg/kg p.o. every 24 hours.

Gabapentin (Neurotonin)

- The mechanism of action is unclear.
- Useful for neuropathic pain, allodynia and hyperalgesia.
- Dose: 1.25–10 mg/kg p.o. every 24 hours in dogs and cats.

Tricyclic antidepressants

- The mechanism of action is unclear; generally thought to be inhibition of the reuptake of the neurotransmitters noradrenaline (norepinephrine), dopamine or serotonin by nerve cells.
- Aid in the treatment of neuropathic pain and pruritus.
- Examples: Amitriptyline in dogs is dosed at 1–2.2 mg/kg p.o. every 12–24 hours, and in cats at 2.5–12.5 mg total dose p.o. every 24 hours. Imipramine in dogs is dosed at 0.5–1 mg/kg p.o. every 8 hours, and in cats at 2.5–5 mg total dose p.o. every 12 hours.

Paracetamol/acetaminophen

- Cox-3 inhibitor, which elevates the pain threshold. So far the Cox-3 enzyme has only been observed within the CNS.
- Can be used with opioids and NSAIDs. Codeine has been used successfully with paracetamol at 1–2 mg/kg p.o. every 6 hours in dogs. *This drug must not be used in cats due to fatal toxicity.*

Benzodiazepines

- Anxiolytics and muscle relaxants.
- Not analgesic in themselves but can be used for pre-anaesthetics in the critically ill or severely stressed patient.
- Example: Diazepam in dogs is dosed at 0.5–2 mg/kg p.o. every 8 hours, and in cats at 1–2 mg p.o. every 8–12 hours, i.v. 0.1–0.25 mg/kg.

Methocarbamol (Robaxin)

- Skeletal muscle relaxant.
- Not analgesic but will decrease muscle spasm and associated pain.
- Methocarbamol in dogs is dosed at 15–20 mg/kg p.o. every 8 hours, and in cats at 20–40 mg/kg p.o. every 8–12 hours.

Bisphosphonates

- Drugs that block osteoclast activity, e.g. pamidronate. In combination with an NSAID alleviates bone pain and diminishes pathological bone turnover in some cases of canine appendicular osteosarcoma and multiple myeloma.
- Oral form alendronate is available in 10 mg tablets.

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Cancer nutrition

General principles of clinical nutrition

'Simple' or uncomplicated starvation

Simple starvation differs from the metabolism of the critically ill, because long periods of food deprivation can be tolerated by the body's coping mechanisms, using hepatic glycogen, triglycerides within adipocytes and amino acids (skeletal muscle, visceral protein). Hepatic glycogen stores are depleted within 12 hours and glucose and insulin decrease initially. There is increased glucagon to stimulate glycogenolysis, and gluconeogenesis is also increased. As glucagon increases, lipolysis increases. This leads to increased glycerol, ketones and free fatty acids (FFAs). The basal metabolic rate (BMR) is downregulated to protect lean body mass. When glycogen sources are gone, amino acids are used for gluconeogenesis. Fat-derived fuels are used instead of glucose in tissues where this is metabolically possible (Mauldin & Davidson 2003).

'Complicated/stressed' starvation (metabolism of the critically ill)

Stressed starvation occurs when the body is in a hypermetabolic state as a result of a traumatic or inflammatory insult. Hypermetabolism compromises the normal metabolic adaptations to starvation that occur in simple starvation. Hormonal changes (increased catecholamine, cortisol, ACTH, glucagon, growth hormone) occur which lead to an increased BMR. An increased BMR, along with an increased need for clotting factors, acute phase proteins, white blood cells and other inflammatory components all increase the demand for glucose and amino acids to such a degree that lean body mass cannot be spared from catabolism, as it would be in simple starvation (Mauldin & Davidson 2003).

Nutritional support is required to prevent malnutrition and a compromised immune function, decreased wound healing, catabolism of lean body mass and likely a negative impact on overall survival (Chan & Freeman 2006). Often energy demands are not met without nutritional intervention, due to anorexia, decreased absorption, vomiting, etc. A high protein intake (up to 50%) is needed to provide the critically ill dog or cat with enough amino acids to stop catabolism of body protein (Donoghue 1989). This may be especially important in the cat, where a lack of amino acids may be responsible for impaired hepatic lipid release, leading to hepatic lipidosis. Fat is the main energy source for most tissues during complicated starvation, whereas carbohydrate may not be used with maximal efficiency due to persistent glucose intolerance and hyperglycaemia (mostly due to peripheral insulin resistance) (Mauldin & Davidson 2003).

In humans, providing nutrition decreases urinary nitrogen loss, stimulates immune function, reverses hypometabolism and provides sustenance during hypermetabolism. This improves recovery, lowers mortality and improves response to trauma and stress. The goal of providing nutrition in animals is to prevent catabolism of tissue proteins (Donoghue 1992). Enteral nutrition (assisted or voluntary) supports the integrity of the gastrointestinal tract (GIT) (Armstrong et al 1990, Robben et al 1999).

When to intervene to ensure adequate nutrition?

Nutritional support should be pre-empted (e.g. anticipated anorexia of more than 3–5 days, trauma, sepsis, peritonitis, pancreatitis, burns, large wounds, major gastrointestinal (GI) surgery, protracted vomiting, diarrhoea). Late signs of malnutrition are weight loss (>10%), poor hair coat, muscle wasting, hypoalbuminaemia, lymphopenia, coagulopathy and inadequate wound healing. Intervention such as placement of a feeding tube or parenteral nutrition should be given prior to these signs (Chan & Freeman 2006). Animals with hypoalbuminaemia are better treated with earlier intervention, as hypoalbuminaemia reflects a prolonged period of malnutrition (Withrow & Vail 2007).

What are the benefits of providing nutritional support to the cancer patient?

The benefits of dietary support in cancer patients include increased tolerance to surgery, chemotherapy and radiation therapy, improved immune function, immunoglobulin and complement levels, and phagocytic function of white blood cells (Ogilvie & Vail 1990).

Metabolic alterations that occur with cancer

Carbohydrate metabolism

Carbohydrate metabolism is significantly different in dogs with cancer; tumour cells preferentially metabolize glucose (carbohydrate) for energy and make lactate (lactic acid) as an end product. Lactate must then be converted back to glucose, which consumes energy and gives a net energy gain to the

tumour and a net loss to the animal, contributing to cancer cachexia. Dogs with lymphoma and a wide variety of malignant diseases have elevated resting insulin and lactate levels compared to control animals. Elevated lactate and glucose levels may persist when dogs are rendered free of cancer with chemotherapy and surgery (Ogilvie & Marks 2000).

Protein metabolism

Tumours often use amino acids preferentially for energy via gluconeogenesis. If protein intake/absorption does not keep pace with use, a negative nitrogen balance occurs. This is seen clinically as muscle wasting, decreased immune function and GI function, and poor wound healing. Decreased body muscle mass, decreased skeletal protein synthesis, increased skeletal protein breakdown and increased liver and whole body protein synthesis all occur to support tumour growth (Ogilvie 2001).

Fat metabolism

Tumour cells have a limited ability to use fat for energy, compared to carbohydrates and protein. Dogs with cancer therefore burn their fat reserves as an energy source. Loss of body fat accounts for the majority of weight loss in people and rodents with cancer cachexia. The type of fat in the food is important, and omega-3 fatty acids have many clinical benefits (Ogilvie 2001, Ogilvie & Marks 2000).

Dogs with cancer without weight loss

In the authors' experience, these dogs form the majority of patients seen in referral veterinary oncology practice, perhaps because many die of their cancer before they become cachectic. Dogs with cancer and no weight loss still show the alterations in protein, carbohydrate and fat metabolism as described above, without any evidence of clinical signs (Ogilvie 2001). Several studies have found no significant differences in resting energy expenditure (and presumably caloric requirements) in dogs with a wide range of malignancies when compared with healthy, client-owned dogs. This finding suggests that, in general, dogs with cancer and no evidence of weight loss do not have energy requirements higher than those of apparently healthy dogs without cancer (Ogilvie 2001). However, the source of their dietary energy may be more critical than their net energy requirements.

Dogs with cancer and weight loss

The first clinical signs of these metabolic alterations are anorexia, mild weight loss, lethargy and an increased susceptibility to side effects of chemotherapy, radiation therapy, surgery, etc. (Ogilvie 2001). A prolonged state of metabolic derangement resulting in accelerated starvation and profound malnourishment is termed 'cancer cachexia'. Decreased nutritional intake/assimilation, abnormal nutrient losses, treatment-related factors, abnormal metabolic pathways and competition with the tumour for nutrients all contribute. End-stage cancer cachexia is characterized by marked muscle wasting, weight loss, debilitation, weakness, loss of body fat stores and lethargy (Ogilvie & Marks 2000) (**Figure 12.1**).

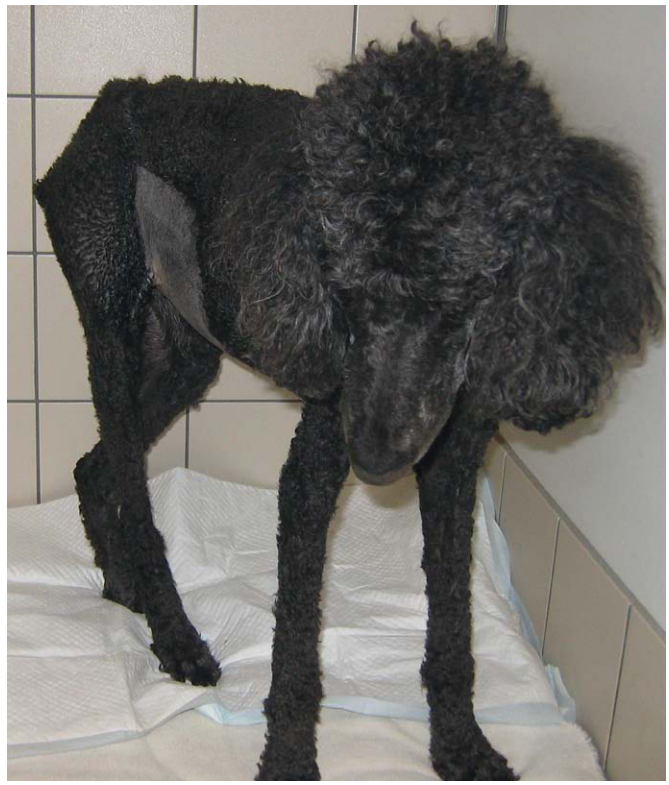


Figure 12.1 Canine patient with cancer cachexia.

In the authors' experience, advanced cancer cachexia is not seen commonly. When it has been seen, it has tended to affect dogs with a significant ongoing, progressive, uncontrolled and often end-stage tumour burden. Overt cancer cachexia is a poor prognostic sign, as patients have a decreased quality of life, decreased response to therapy and shortened survival time compared to those with similar diseases without cachexia (Ogilvie 2001). Dogs with cancer may develop cachexia despite a nutritional intake considered adequate for a normal dog (Ogilvie & Vail 1990).

What to feed the cancer patient

The finding that tumour cells tend to use carbohydrate and protein preferentially to lipid for fuel has led to the hypothesis that feeding foods relatively high in fat may be more beneficial than feeding carbohydrate-rich foods. This diet is then designed to 'feed the dog and starve the tumour'. Foods containing less than 30% protein calories and more than 40% carbohydrate calories should be avoided in cancer patients (most commercial foods are suboptimal in this regard) (Ogilvie & Marks 2000).

Carbohydrates

Carbohydrates may be poorly used due to peripheral insulin resistance. Foods high in carbohydrates may increase the total amount of lactate produced and the need for the dog to use energy to convert lactate back to glucose. Soluble carbohydrates should comprise less than 25% of the food's dry matter (or <20% of the daily energy requirement, DER) (Ogilvie & Marks 2000).

Fat

A large proportion of the daily energy should come from fat in the diet because tumour cells have difficulty using fat compared to carbohydrate and protein, and loss of body fat contributes to weight loss and cachexia. Fat should comprise 25–40% of the food's dry matter (50–65% of the DER) (Ogilvie & Marks 2000).

Omega-3 (n-3) fatty acids

Increased levels of dietary n-3 fatty acids may benefit the cancer patient, according to studies that link n-3 fatty acids to tumour inhibition and immune enhancement. N-3 fatty acids have this selective tumoricidal action without harming normal cells. As they also decrease protein degradation without altering protein synthesis, the net effect is anti-cachectic. Dietary levels should be in excess of 5% of the food's dry matter, with an n-6 : n-3 ratio of <3.0 (Ogilvie & Marks 2000).

Omega-6 (n-6) fatty acids

Metastases are enhanced with omega-6 (n-6) fatty acids (Ogilvie & Marks 2000).

Protein

This is used to build body protein (muscles) and for immune function. Dietary protein should be fed at greater levels than those required in a normal dog to help prevent a loss of muscle mass. Protein should comprise 30–45% of the food's dry matter in dogs and 40–50% in cats (25–40% of the DER in dogs and 35–45% of the DER in cats) (Ogilvie & Marks 2000).

Amino acids

Methionine

If methionine is replaced with its precursor homocysteine, methionine-dependent tumour cells are locked into late S and G2 phases of the cell cycle, which increases the percentage of tumour cells sensitive to chemotherapy (Ogilvie & Marks 2000).

Asparagine

Asparagine is essential for tumour growth in lymphoma. Treatment of dogs and cats with L-asparaginase (which breaks down asparagine) has induced complete (but short-term) remissions in up to 80% of dogs and cats with lymphoma (Ogilvie & Marks 2000).

Tyrosine and phenylalanine

Restriction of these amino acids has been reported to suppress melanoma growth in tissue cultures and rodents (Ogilvie & Marks 2000).

Arginine

Adding arginine to total parenteral nutrition solutions decreases tumour growth and metastatic rate in rodent cancer models. Arginine is an essential amino acid for cats and conditionally essential for dogs. Arginine given in large doses exerts numerous beneficial effects on the immune system, particularly on thymus-dependent and T-cell-dependent immune reactions. Arginine should comprise >2% of the dry matter of the food (Ogilvie & Marks 2000).

Glutamine

Glutamine is an essential precursor to nucleotide biosynthesis and is the most important oxidative fuel for enterocytes (Ogilvie & Marks 2000).

Glycine

Glycine reduces cisplatin-induced nephrotoxicity (Ogilvie & Marks 2000).

Vitamins

Retinoids

The synthetic retinoids isotretinoin and etretinate (vitamin A derivatives) have been therapeutic in some dogs with intracutaneous cornifying epitheliomas, other benign skin tumours, cutaneous lymphoma, solar-induced squamous cell carcinoma and associated preneoplastic lesions. The retinoids promote cellular differentiation and may enhance the susceptibility of neoplastic cells to chemotherapy and radiation therapy (Ogilvie & Marks 2000).

Vitamin C

Vitamin C may be therapeutic as an antioxidant, as well as an inhibitor of nitrosation reactions (nitrosamines have carcinogenic capabilities), and for overcoming drug resistance (e.g. vincristine) in some cancer cells. However, few direct data exist proving its efficacy (Ogilvie & Marks 2000).

Vitamin E

Vitamin E (α-tocopherol) is an antioxidant (free radical scavenger) with a broad capacity to inhibit mammary tumour carcinogenesis and colon carcinogenesis in rodents. Vitamin E may normalize the immune system by interacting with macrophages and T lymphocytes to inhibit retroviral-induced infections and retroviral-induced tumorigenesis (Ogilvie & Marks 2000).

Minerals

Selenium

Low selenium levels have been observed in humans with GI cancer. In rodents, dietary supplementation with selenium inhibits colon, mammary gland and stomach carcinogenesis (Ogilvie & Marks 2000).

Iron

Mice with low levels of iron have slower tumour growth than those with normal iron levels. Lung, colon, bladder and oesophageal cancer in people have been highly correlated with increased serum iron levels and increased transferrin saturation (Ogilvie & Marks 2000).

Zinc

Low levels of zinc in blood and diseased tissue have been observed in human oesophageal, pancreatic and bronchial cancer. Zinc deficiency enhances carcinogenesis in rodents (Ogilvie & Marks 2000).

Novel foods

Soybean-derived Bowman-Birk inhibitor

This can inhibit carcinogenesis in vivo and in vitro, and is also associated with increased intestinal integrity in cats given methotrexate (Ogilvie & Marks 2000).

Garlic

Epidemiological studies correlate high garlic consumption with reduced cancer risk, although no studies demonstrate the safety or effectiveness of garlic for prevention or treatment of cancer in dogs, cats or people. There is evidence that garlic has activity against cultured human breast cancer and melanoma cells, without harming normal cells (Ogilvie & Marks 2000).

How to feed the cancer patient

Nutritional support must be individualized.

Hand feeding a variety of foods, heating foods, adding flavour enhancers, syringe feeding or wiping onto lips/tongue (if the patient will allow) will sometimes get them to start eating on their own. Appetite stimulants, e.g. benzodiazepine derivatives oxazepam, diazepam, cyproheptadine, and supplementing B vitamins may also be useful.

Enteral tube feeding techniques should be considered if efforts to stimulate the appetite fail or if long-term nutritional support (more than a few days) is required. Naso-oesophageal, oesophagostomy or gastrostomy tube are the most efficient and reliable methods. It is better to proactively place a feeding tube during surgery or before radiation therapy is started (for nose, oral cavity, neck) if nutritional support is expected.

Parenteral nutrition is another method of providing nutrients when enteral nutrition would not be tolerated. Enteral feeding is the preferred route of nutrient delivery because it is more physiological, safer and less expensive than total or partial parenteral nutrition. It also prevents villous atrophy, stimulates the production of local antibodies and prevents bacterial translocation from the gut to the systemic circulation. Glutamine can only be provided via the enteral route (Prittie & Barton 2004).

How much to feed the cancer patient

The patient should receive its calorific requirement, which should also meet the nutrient profile required. Critically ill patients generally do not have energy needs that exceed those of healthy dogs (Ogilvie 2001), and the most critically ill patients may be better treated with moderate underfeeding (Chan 2006).

Resting energy requirement (RER) is defined as the number of calories required for maintaining homeostasis at rest in a thermoneutral environment while the animal is in a post-absorptive state (Chan 2005).

- $RER = 70 \times BW^{0.75}$ for animals <2 or >45 kg
- Or, if 2–45 kg, $RER = (30 \times BW) + 70$

BW, the animal's current body weight in kg; RER in kcal (Marks 2005).

RER can be increased by an illness factor of 1.1–2, but care should be taken not to overfeed as this may compromise outcome (Chan 2004). Some nutritionists recommend feeding illness factors ranging from 1.0 × RER for minor conditions to a maximum of 1.4 × RER in the cat and 1.6 × RER in the dog for disease states such as severe thermal burns (Mauldin & Davidson 2003).

In severely malnourished dogs and cats, the goals are to preserve lean body mass and organ function rather than to restore optimal body condition in the acute stages of disease (Chan 2004). The calorific requirement of the critically ill patient is estimated initially to be the RER (Marks 2005). If weight loss continues, the number of calories should be increased by 25% and the plan should be reassessed and readjusted every few days (Chan 2005).

Enteral tube feeding

(See Table 12.1 for caloric density and profile of liquid enteral formulations.)

The general protocol for enteral feeding is to give less than the calculated calorific requirements initially, then gradually increase the amount to ensure patient tolerance to feeding. Even if the calorific requirement isn't met initially, feeding

Table 12.1 Caloric density and profile of liquid enteral formulations*

Product (tinned)	Protein	Fat	Carbohydrate	N-3 fatty acids	Arginine	Kcal/g or ml
Hills a/d	45.7	28.7	17.4	2.6	2.05	1.3/g
Hills n/d canine (moist)	37.9	33.1	20.1	7.3	2.95	1.4/g
Eukanuba max cal	43.3	41.1	7.6	0.78	2.6	2.1/g
Arnolds Fortol	7.6	5.0	4.8	–	–	1.01/ml
Waltham Sensitivity Control	24.0	9.0	35.9	5.14	–	1.2/g
Waltham Convalescence Support	35.0	24.5	–	7.7	–	1.1/g

*Prescription diet product information; nutrients are expressed as % dry matter.

enterocytes directly maintains normal gut structure and function (Kerl & Johnson 2004). On day 1, 25% of the caloric requirement is fed, on day 2 this is increased to 50%, then 75% on day 3, then 100% on day 4. Food is warmed to room temperature prior to feeding, and the tube is flushed with about 10 ml of warm water after each feed to prevent blocking (Marks 2005). Animals should be comfortable and show no signs of distress when receiving tube feeding.

The method of tube feeding selected depends upon the anticipated duration, the risk of aspiration or reflux, tolerance for anaesthesia and the condition of the GI tract (Prittie & Barton 2004).

Naso-oesophageal

This is the least invasive method of tube feeding (**Figure 12.2A**). However, this method is contraindicated if there is facial trauma, abnormal gag reflex or other predisposition to aspiration pneumonia such as oesophageal dysfunction or persistent vomiting. Voluntary intake may decrease due to pharyngeal irritation.

The technique for placing a naso-oesophageal tube is outlined in Box 12.1.

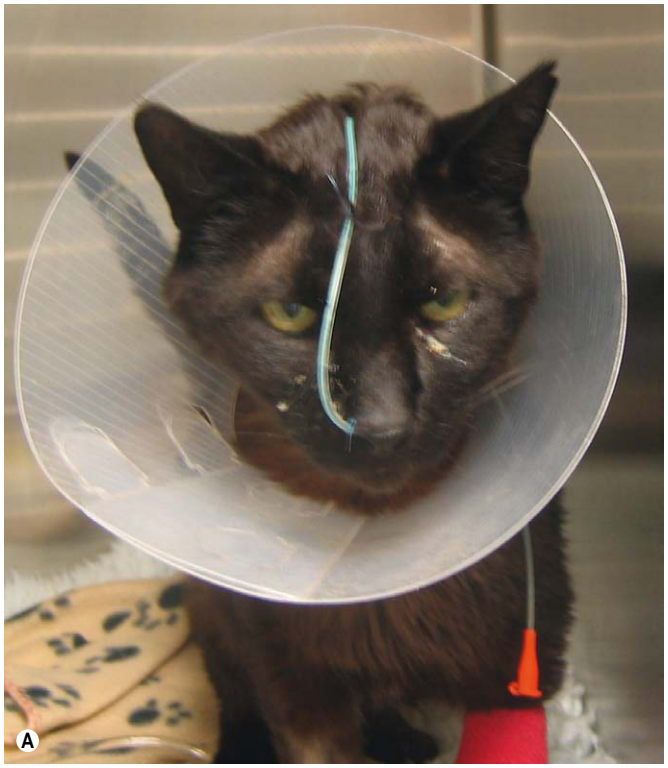
Oesophagostomy

Oesophagostomy (**Figure 12.2B**) is minimally invasive and may be used for long-term feeding. In the study by Crowe & Devey (1997), oesophagostomy tubes were maintained for up to 557 days. All patients healed well after tube removal, with no evidence of stricture or fistula. Most diets can be fed through larger oesophagostomy tube lumens (5–30 FG range) and the tubes are generally well tolerated. Feeding can start straight away, and the tube can be removed the same day without concern for leakage (Crowe & Devey 1997).

Contraindications include oesophageal disease/surgery. Complications include damage to neurovascular structures during placement, vomiting, gastroesophageal reflux, oesophagitis, peristomal infection, and tube kinking or displacement with vomiting. Stricture is possible but has never been documented. Peritonitis is not a risk, an advantage over gastrostomy and jejunostomy tubes.

The required daily volume of food is divided into 4–6 bolus feeds. Do not give more than 10 ml/kg in 5 minutes, and no more than 30 ml/kg at a time (Crowe & Devey 1997). Maximum fed per meal was 60 ml in a study of 60 cats (Levine et al 1997).

The technique for placing an oesophagostomy tube is outlined in Box 12.2.



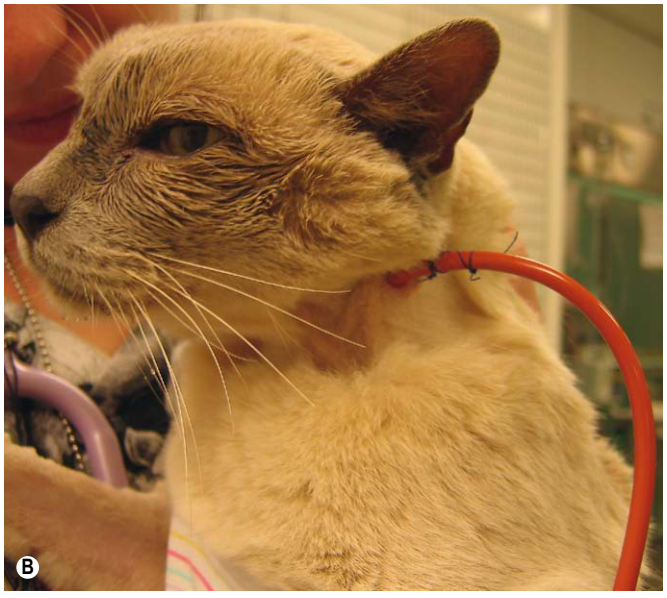


Figure 12.2 Cats with (**A**) naso-oesophageal feeding tube and (**B**) oesophagostomy tube.

Gastrostomy (percutaneous endoscopy gastrostomy, PEG) tubes

These are mushroom-tipped feeding tubes, indicated if the oral cavity, pharynx or oesophagus is to be bypassed. They have a very large tube bore so can feed any blenderized diet. Contraindications include primary gastric disease, persistent vomiting or pancreatitis. Use with caution if a dysfunctional oesophagus or abnormal mentation is present due to a high risk of aspiration.

Patients can eat voluntarily with the tube in place. If long-term use is planned (although it can be maintained for up to 438 days; Elliot et al 2000), the PEG tube can be replaced with a low profile feeding device (LPFD) after the development of a mature gastrocutaneous fistula. LPFD is like a big flat button, with less chance of being dislodged and greater freedom of movement. PEG tubes can be placed surgically or by endoscopy. Surgical placement has the advantage of ensuring correct tube placement by directly visualizing the stomach wall, and

Box 12.1

Naso-oesophageal tube placement technique

1. Lubricate the tube tip with lidocaine jelly, and numb nose with lidocaine drops.
2. Measure from nose to xiphoid. Using an angiography guide wire placed locally in the nostril, aim ventromedially. Do not go into the stomach; access should be between the 7th and the 9th rib on radiographs.
3. Ensure that the tube is not placed down the larynx/trachea instead of the oesophagus. Check by looking at the larynx with a laryngoscope under light sedation, inject 5–10 ml of air down the tube and auscultate for borborygmi, or inject a small volume of sterile saline (3–5 ml) to elicit a cough if the tube is in the trachea.
4. Suture the tube in place, take a radiograph to ensure correct placement, and place an E-collar to prevent self-trauma.
5. When commencing feeding, use liquid feed due to the small diameter of the tube: 3.5–5 FG (French gauge) in cats, 5–10 FG in dogs.

Box 12.2

Oesophagostomy tube placement technique

1. Anaesthetize, intubate and place the animal in right lateral recumbency (cranial cervical oesophagus in on the left), clip and prepare the skin of mid-cervical region.
2. Measure the length of tube (so that distal end will be at the 7th to 10th ribs or mid-oesophagus), and mark on the tube the point where it will exit the skin (mid-cervical region).
3. With one hand, place a large pair of curved haemostats into the oesophagus via the mouth. Push up on the tips of the haemostats firmly laterally (left) to tent the skin.
4. With the other (sterile) hand, palpate the tips of the haemostats and use a scalpel blade to cut a small hole through the skin overlying the haemostat tips. Carefully cut the subcutaneous fat to expose the oesophageal wall and make a small hole so that just the tips of the haemostats poke through the oesophageal wall and the skin.
5. The distal end of the feeding tube is then placed into the jaws of the haemostats and pulled out of the mouth, the proximal end of the tube still exiting the cervical incision.
6. The distal end of the tube is then grasped with the haemostats and the tube redirected back down the oesophagus (the proximal end of the tube may need to be pulled out of the cervical incision to facilitate this). The end of the tube should be at the level of the mid-oesophagus, avoiding the lower oesophageal sphincter (as this stimulates vomiting).
7. A stylet or guide wire or endoscope may be useful to ensure the tube is not kinked.
8. The proximal end of the feeding tube is sutured to the skin using a finger-trap suture. The tube can also be anchored to the periosteum at the wing of the atlas (Crowe & Devey 1997).
9. The stoma site is bandaged and the bandages changed daily.

Box 12.3

Gastrostomy tube placement technique

1. The dog is anaesthetized and intubated and placed in right lateral recumbency, and the left paracostal region clipped and prepped for surgery.
2. An assistant places a large, stiff, orogastric tube into the stomach until it is visualized and palpable against the abdominal wall.
3. The skin and abdominal muscles are incised using a scalpel blade over the tube lumen, and the stomach wall is visualized and palpated.
4. Stay sutures are placed in the stomach wall and tension is maintained on these to ensure stomach contents are not leaked into the abdominal cavity.
5. A purse-string of 2-0 PDS or similar is placed (sutures should engage the full thickness of the stomach wall).
6. A small hole is made in the stomach wall and the mushroom-tip feeding tube is introduced.
7. The purse-string is tightened around the tube.
8. The stay sutures are removed and the stomach wall is pexed to the abdominal wall with sutures either side (or in a box) around the tube. Sutures engage the full thickness of the stomach wall and abdominal fascia.
9. If any stomach contents were leaked into the abdomen, the abdominal cavity is lavaged prior to closure.
10. Omentum can be interposed between the stomach and the abdominal wall to help form a seal.
11. The laparotomy wound is closed and the tube exits the skin via a skin incision adjacent to the laparotomy wound, and the tube is also sutured to the skin with a finger-trap suture.
12. The area is bandaged and changed as needed.

can be done by a limited flank approach. The technique for placing a gastrostomy tube is outlined in Box 12.3.

Endoscopic placement has the disadvantages of limited visualization (and thus the possibility of spleen laceration or intestinal laceration, especially in deep-chested dogs). In addition, as there is no pexy of the stomach to the abdominal wall, rather a reliance on adhesion formation, early inadvertent tube removal is a major complication. Endoscopically placed tubes can also induce stomach wall necrosis by excessive tension, and tubes can migrate with inadequate tension.

Other complications (regardless of method of placement) include obstruction of tube, stomal infection (in one study 46% of dogs developed renal failure due to impaired immune function, increased risk of infection and delayed wound healing associated with uraemia and malnutrition; Elliot et al 2000), vomiting, diarrhoea, regurgitation, aspiration, and the potential for peritonitis if inadequate adhesions have formed.

The tube should be left in for a minimum of 7–10 days, preferably 14 days if removed by traction (versus cutting off the mushroom tip to pass in faeces). The mushroom tip can be cut off and retrieved endoscopically if there is concern about the tip causing intestinal obstruction in smaller animals. Tube size is 16–20 FG in cats and small dogs, 24–32 FG for larger dogs.

Feeding is delayed for 24 hours to allow for return of stomach motility and formation of a fibrin seal. The required daily volume of food is divided into 4–6 bolus feeds.

Jejunostomy

Jejunostomy is used to bypass the oesophagus, stomach, duodenum and pancreas. Indications for use are as for duodenostomy. As jejunostomy bypasses the pancreas it is useful for

Box 12.4

Jejunostomy tube placement technique

1. A 12–14 G hypodermic needle is passed through the skin, abdominal wall and into the abdominal cavity, and the feeding tube is introduced into this hole. A segment of jejunum is selected which will join to this hole without tension.
2. A purse-string suture is placed in the antimesenteric jejunal wall (using 3-0 to 4-0 PDS or similar) and a 12–14 G hypodermic needle is pushed obliquely to travel in a subserosal tunnel for 2–3 cm.
3. The needle is removed and the feeding tube is directed into the tunnel, which guides tube placement. Ensure an adequate length of tube within the intestinal lumen (20–30 cm).
4. The purse-string suture is tightened.
5. The jejunum around the purse-string is then pexed to the abdominal wall using 3-0 PDS or similar. (The full thickness of the intestinal wall and abdominal fascia must be engaged for strength of pexy.) The omentum can be placed between the intestine and the abdominal wall to help seal and promote healing.
6. The feeding tube is also sutured to the skin with a finger-trap suture.

pancreatitis, and is also useful if there is an increased risk of aspiration. Although feeding (liquid diet) can begin several hours after tube placement, constant rate infusion (CRI) feeding is preferred. Complications include peritonitis, diarrhoea, vomiting, stoma site infection and tube obstruction.

The feeding tube is 3.5–5 FG, 36 inches long. Avoid stiff polyvinyl catheters as they have a higher incidence of kinking and intestinal perforation. The technique for placing a jejunostomy tube is outlined in Box 12.4.

The CRI is 1 ml/kg/hr initially, at 30–50% of the calculated caloric requirement. A slow increase to 100% caloric requirement is preferable to bolus feeding if possible.

Jejunostomy tubes can be placed through gastrostomy tubes, allowing food to be dispensed directly into the mid/distal jejunum without the need for a jejunostomy (Jergens et al 2007).

Duodenostomy

Duodenostomy tube placement has been described, and is worth considering if the animal is not a good candidate for general anaesthesia or gastrostomy or oesophagostomy tube feeding, or if being ventilated. The tube actually enters the jejunum (Novo et al 2001).

Parenteral feeding

Enteral nutrition (EN) is preferable to parenteral feeding, as it is more physiologically sound (preserves the GIT mucosal barrier, prevents GIT and pancreatic enzyme suppression) and is cheaper, safer and more convenient (Crowe & Devey 1997). However, parenteral nutrition (PN) can supply amino acids and calories and correct malnourishment (Shizgal 1993). It is also useful to be given pre-emptively to prevent malnutrition when oral or enteral intake is not adequate or possible. PN and EN can be combined, if even a small amount of EN would be tolerated (Chan 2005).

PN is given as intravenous constant rate infusions via fluid pumps. PN is formulated as a mix of carbohydrate (dextrose), lipid and amino acids (Chan & Freeman 2006). Results of studies suggest that the i.v. amino acid requirement of clinically normal dogs is approximately 2.3 g/kg/day (Mauldin et al 2001), and provision of crystalline amino acid solutions is essential to maintain a positive nitrogen balance and the lean body tissues (Chan & Freeman 2006). Lipid emulsions are the calorically dense component of PN and a source of essential fatty acids. Daily multivitamins are also added. Vitamin K can be given for longstanding malnutrition/malabsorption. Trace elements can also be added after 5 days of PN (Chan & Freeman 2006).

To prevent PN-related infections, it is given via a closed system to maintain sterility, and not disconnected for walks or diagnostics. Intravenous catheters for exclusive PN use are placed and continuously handled aseptically using strict aseptic technique. Each line etc. is changed daily (Chan & Freeman 2006).

Critical care patient monitoring is required, with frequent assessment of haematology, biochemistry and electrolytes. Before starting parenteral feeding, serum biochemistry and ammonia and a urinalysis should be carried out to ensure correction of hydration, electrolyte or acid–base balance and haemodynamic status. Ascertain if the patient is hyperglycaemic, hypertriglyceridaemic or hyperammonaemic, or has concurrent renal, cardiac or hepatic disease, all of which influence formulation of PN diets (Chan 2005).

Total parenteral nutrition (TPN)

TPN is designed to meet 100% of energy requirement (ER). It must be given through a central vein (usually by a jugular venous catheter) because it is hyperosmolar. TPN starts as 50% of RER on day 1, then increased to target amount on day 2 (Chan & Freeman 2006).

Partial parenteral nutrition (PPN)

PPN can be given into a peripheral vein as it has a lower osmolarity by diluting to <800 mOsm/l. PPN provides 40–70% of ER, so is insufficient alone for nutritional intake. 5% dextrose is used instead of 50% dextrose, and addition of hypo- or isotonic crystalloids. PPN is intended for short-term use (<5 days). PPN is started without a gradual increase (Chan & Freeman 2006).

PN should be stopped when the animal has at least 50% of RER as assisted or voluntary enteral feeding. PPN can be stopped abruptly, but TPN should be stopped over 6–12 hours (Chan & Freeman 2006).

Complications of PN include catheter kinking, occlusion, etc. (as for any i.v. fluid therapy), metabolic complications (hyperglycaemia, hypertriglyceridaemia, hyperbilirubinaemia, increased alkaline phosphatase activity, azotaemia, electrolyte shifts and hyperammonaemia) and infection. Hypertriglyceridaemia and hyperglycaemia are the most common metabolic complications and are usually controlled by reducing the rate of infusion for 12–24 hours, or reformulating the diet. Phlebitis ± systemic sepsis is reported in 3–12% of dogs and cats on PN. Remove and culture any catheter if suspected of causing infection (fever or increased white cell count). PPN has fewer complications than TPN (Chan 2005).

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Tumours of head and neck

CANINE TUMOURS

Oral tumours

Epidemiology

Tumours of the oral cavity of dogs account for approximately 6% of all tumours (Hoyt & Withrow 1984). They commonly arise from the gingiva but can arise from buccal mucosa, mandible, maxilla, palate, dental structures, tongue and tonsils.

A number of histological subtypes are recognized and as the prognosis and treatment options depend upon the histological diagnosis, early biopsies are recommended:

- *Epithelial*: squamous cell carcinoma (SCC), papilloma, fibropapilloma, intraosseous carcinoma and invasive nasal carcinoma
- *Melanocytic*: malignant melanoma (MM)
- *Mesenchymal*: fibrosarcoma (FSA), fibroma, rhabdomyosarcoma (rare), haemangiosarcoma (HSA), granular cell tumour (or myoblastoma), mixed mesenchymal sarcoma, neurofibrosarcoma, anaplastic sarcoma, myxosarcoma, chondrosarcoma (CSA), osteosarcoma (OSA), multilobular osteochondrosarcoma (MLO)
- *Miscellaneous*: transmissible venereal tumour (TVT), mast cell tumour (MCT), lymphoma (LSA), plasmacytoma.

For odontogenic tumours, the following tissues should be sampled:

- *Epithelial*: ameloblastoma, keratinizing ameloblastoma (cats only), ameloblastic adenomatoid, calcifying epithelial odontogenic tumour, hamartoma, dentinoma, odontoma, inductive fibroameloblastoma (cats only)
- *Mesenchymal*: fibromyxoma, cementoma, odontogenic fibroma
- *Periodontal*: acanthomatous epulis, ossifying epulis, fibromatous epulis.

Signalment

In general these are tumours of older dogs, except FSA seen in large breed dogs (e.g. German Shepherds, Golden Retrievers and Labrador Retrievers), papillary SCC seen in dogs of less than 6 months of age (Ogilvie et al 1988), undifferentiated malignancy of young dogs (less than 2 years) and viral-induced papillomatosis (less than 1 year). MM and FSA are more common in male dogs (Dorn et al 1968).

The breeds most commonly affected with oral tumours are Cocker Spaniels, Poodles, Weimaraner, German Shepherds, Golden Retrievers, German Shorthaired Pointers and Boxers (Cohen et al 1964, Dorn & Priester 1976, Todoroff & Brodey 1979). Small breeds are at a higher risk of MM and tonsillar carcinomas. Dogs with heavily pigmented oral mucosa are predisposed to MM (Dorn & Priester 1976, Dorn et al 1968).

Clinical signs

The clinical signs include decreased appetite, halitosis, loose/missing teeth, bloody saliva, exophthalmos, epistaxis, dysphagia, difficult/painful mastication and psychogenic polydipsia. Rostral tumours are most likely to by seen by the client and therefore diagnosed sooner than more caudally located tumours. Dyspnoea is common with large tonsillar, posterior pharyngeal tumours or lymphadenopathy.

Diagnostic work-up of the patient with an oral tumour

Imaging

Radiographs

Intraoral (best), open mouth, oblique lateral, dorsoventral (DV) and ventrodorsal (VD) to determine the extent of bone lysis but occasionally bone reaction is proliferative (e.g. OSA). The presence of no bony lysis on radiographs does not mean that there is no bony involvement. Radiographs underestimate the extent of bone destruction as lysis is only observed when more than 30–40% cortical bone loss has occurred. Fixation of tumour to bone suggests microscopic invasion of bone.

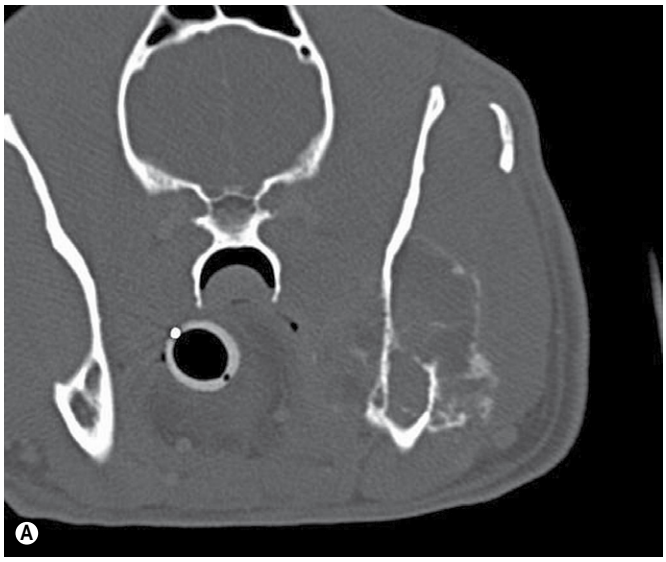
Computed tomography (CT)

The limitations of oral radiographs mean that CT is a much more sensitive diagnostic tool when considering the extent of local bone invasion prior to treatment and should be recommended when possible (**Figure 13.1**). Thoracic radiographs/CT are indicated for staging purposes.

Biopsy

- Large incisional (wedge) – at edge and centre of lesion
- Planned to minimize contamination of normal tissue
- Cytological preparation is usually unrewarding
- Cautery after biopsy may be required.

Routine blood work, haematology and biochemistry are indicated, plus urinalysis.



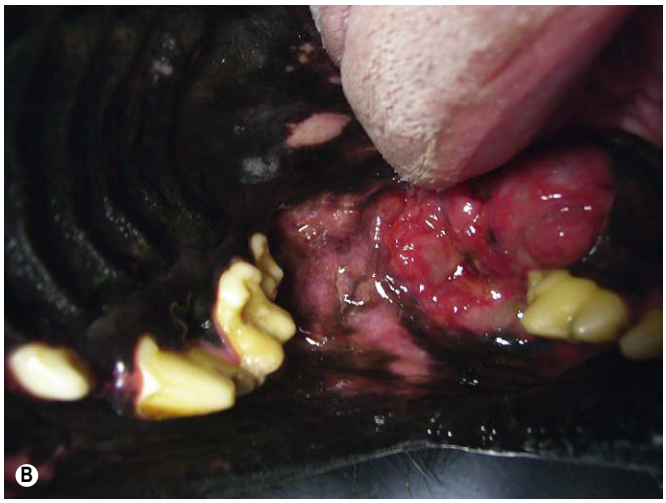


Figure 13.1 (**A**): CT scan of a dog with a large mandibular squamous cell carcinoma. (**B**) Dog before radiotherapy and surgery.

Staging (see Table 13.1)

- Staging is based on the size of the primary tumour, regional lymph node (RLN) involvement and distant metastasis.
- Fine needle aspiration (FNA) or excisional biopsy of the RLN is necessary if it is enlarged, fixed or painful.
- Thoracic radiographs or CT for staging.

Clinical staging grouping (see Table 13.2)

Most dogs have stage III or IV disease at diagnosis.

Treatment

Surgery

The treatment of choice for the majority of oral tumours is surgical excision with margins. The margins required and the application of adjunctive therapy depend on histological diagnosis.

Radiotherapy

After surgery, radiotherapy is the most successful modality in the management of oral tumours in dogs.

Table 13.1 World Health Organization (TNM) classification system for canine tumours of the oral cavity

Stage	Characteristics
T – Primary tumour	
T0	No evidence of tumour
Tis	Carcinoma in situ
T1	<2 cm (1a = no bony invasion, 1b = bony invasion)
T2	2–4 cm (2a, 2b)
T3	>4 cm (3a, 3b)
N – Regional lymph nodes	
N0	No regional lymph node (RLN) involvement
N1	Movable ipsilateral RLN (N1a = no tumour cells, N1b = tumour cells)
N2	Movable contralateral or bilateral RLN (N2a, N2b)
N3	Fixed RLN
M – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

(With permission from the World Health Organization.)

Table 13.2 WHO Clinical staging of patients with oral tumours

Stage	Tumour, node, metastasis
I	T1 N0–2a M0
II	T2 N0–2a M0
III	T3 N0–2a M0
IV	T1–3 N2b–3 M0, T1–3 N0–3 M1

The World Health Organization staging scheme for dogs with oral melanoma is based on size, with stage I =<2 cm diameter tumour, stage II = 2 to <4 cm diameter tumour, stage III => or = 4 cm tumour and/or lymph node metastasis, and stage IV = distant metastasis.
(With permission from the World Health Organization.)

- Radiation can be used as adjunctive therapy to clean up 'dirty' margins from incompletely resected MM, SCC, FSA, acanthomatous epulis, plasmacytoma, etc.
- Inoperable tumour of any histological type (palliative).
- As sole treatment for certain small tumours, e.g. plasmacytoma, acanthomatous epulis, MM and isolated LSA. Success of radiotherapy depends on histological type and clinical stage.

Chemotherapy

Chemotherapy has little application for oral tumours with the exception of LSA and plasmacytomas, but may have some role in the management of SCC in combination with the above modalities.

Malignant melanoma

This is the most common oral tumour in dogs and accounts for 30–40% of all oral malignancies (Bradley et al 1984, Dorn & Priester 1976, Todoroff & Brodey 1979). Typically seen in

older dogs (mean age 12 years) (Ramos-Vara et al 2000) with possible sex predilection for males (Bjorling et al 1987, Dorn & Priester 1976, Todoroff & Brodey 1979). Dogs with heavily pigmented mucosa are at greater risk (Dorn & Priester 1976, Dorn et al 1968) and Chow Chow and Golden Retriever were over-represented in one study (Ramos-Vara et al 2000).

The site for these tumours is gingiva (42–63%), buccal or labial mucosa (15–33%), hard or soft palate (10–16%) and tongue (1.5–3.3%) (Dorn & Priester 1976, Todoroff & Brodey 1979). The tumour often appears firm and black (**Figure 13.2**) but 33% are unpigmented. It is not uncommon to have surface ulceration and necrosis. MM is rapidly growing and locally invasive.

Radiographic evidence of bone involvement is seen in 57% of patients at the time of diagnosis (Todoroff & Brodey 1979) and pulmonary metastases in 14% of cases. RLN metastasis has occurred in 53–74% of cases (Todoroff & Brodey 1979, Williams & Packer 2003). A RLN may be of normal size on palpation, but still be positive for metastasis (Williams & Packer 2003).

Amelanotic MM is the most probable tumour on any biopsy read as anaplastic or undifferentiated sarcoma or carcinoma. In such cases additional stains are required to confirm the origins of the tumour. Melan A (an immunohistochemical marker) was detected in 113/122 (92.6%) of oral MM (Ramos-Vara et al 2000).

Prognosis

Median survival times (MST) for dogs with oral melanoma treated with surgery are approximately 17–18, 5–6 and 3 months with stage I, II and III disease, respectively (Bergman 2007). Overall, 35% of patients with MM treated with mandibulectomy or maxillectomy will survive more than 1 year (Withrow & MacEwen 2001).

Prognostic indicators include:

- Stage (Blackwood & Dobson 1996, MacEwen et al 1986, Théon et al 1997a).
- Size (<2 cm, MST was 511 days compared with 164 days if >2 cm or positive RLN) (MacEwen et al 1986). Smaller tumours are also more amenable to local control with radiotherapy (Blackwood & Dobson 1996, Théon et al 1997a).
- Ability of first treatment to give local control.
- Recurrence of MM after surgery negatively impacts on survival times.
- Location within the oropharynx may affect survival rates in that patients with tumours located on the lip or buccal mucosa develop metastasis late and are less likely to have positive lymph nodes at the time of presentation. Rostral mandibular sites also have a better prognosis than other locations (Hahn et al 1994, Kitchell et al 1994). Location influenced prognosis following multimodal therapy (curative intent surgery, palliative surgery, radiotherapy, chemotherapy, tumour vaccine therapy, gene therapy and immunotherapy), with MM of the lip surviving a median of 580 days, tongue 551 days, maxilla 319 days and hard palate 330 days. Small pedunculated melanomas on the gum or lip line are expected to behave better than larger intraoral MM (Withrow & MacEwen 2001).
- Histological criteria: Spangler & Kass (2006) described melanocytic oral neoplasms in 73 dogs; 92% of these were classified as malignant in the biopsy report, but malignant behaviour (i.e. metastasis or recurrence) was observed in only 59% of cases. A prognostic model based on nuclear atypia provided the most accurate (89%) prediction of overall behaviour. Another paper found a histological proliferation index (MIB-1) correlated with prognosis, as did lymphatic invasion for oral and cutaneous MM (Millanta et al 2002).

Indicators that are not prognostic: age, breed, sex, degree of pigmentation, microscopic appearance (with routine histological assessment) and DNA ploidy.

The prognosis is poor to fair, as 95% of dogs will eventually develop metastatic disease. With no treatment, the MST is 65 days (Harvey et al 1981). Metastatic rate is site, size and grade dependent.

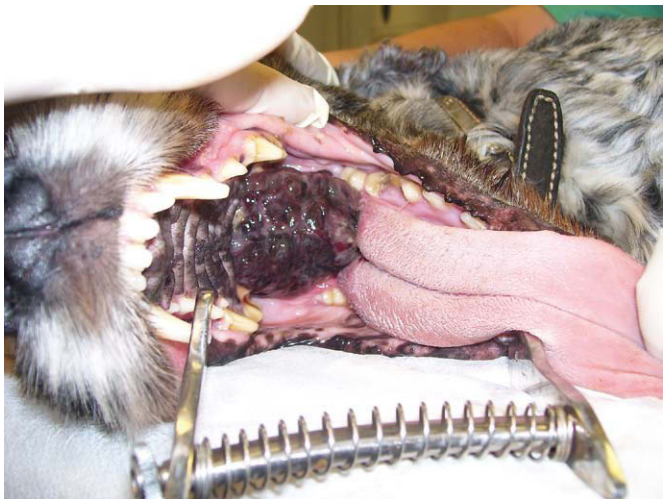


Figure 13.2 Palatal melanoma.

Treatment

Surgery

The treatment of choice for oral MM is surgical excision with wide margins. This means that for patients with gingival tumours mandibulectomy or maxillectomy is indicated. A number of retrospective studies have evaluated the survival rates of dogs undergoing surgery alone. One recent study showed that in 78 dogs the MST was 20 months for dogs with stage I and II disease and 6 months for stage III and IV. This emphasizes the value of early detection and appropriate treatment. Earlier studies reported an MST of 9–11 months with a 12-month survival rate of 21% and a recurrence rate of 22% for dogs undergoing mandibulectomies. For maxillectomies the MST was 4.5–10 months, a 12-month survival rate of 27% and a recurrence rate of 48% (Kosovsky et al 1991, Schwarz et al 1991a).

The above illustrates the higher recurrence rate with maxillary tumours. Morbidity is greater with more extensive surgery. Client satisfaction with cosmetic and functional outcome is generally high (85%) (Fox et al 1997). Problems include dehiscence, recurrence and metastasis.

It is to be emphasized that surgical success is dependent not only upon the size and location of the tumour, but also the skill and experience of the surgeon and, as such, the above is not always representative.

Prognosis with radiotherapy

MM responds well to radiotherapy (83–100% response rate with up to 70% having a complete response) (Bateman et al 1994a,b, Blackwood & Dobson 1996, Freeman et al 2003, Théon et al 1997a). Typically a coarse fractionation protocol is used (3–4 fractions of 8–9 Gy).

The use of radiation in the management of oral MM depends on the size, location and goals of treatment for each patient. Proulx et al (2003) compared a number of radiation protocols and showed no significant difference in survival times based on protocol (9 Gy × 4 fractions, 10 Gy × 3 fractions, or 2–4 Gy × 12–19 fractions).

A number of studies have also looked to evaluate the efficacy of platinum-based chemotherapy in conjunction with radiation, but unfortunately results to date have shown no survival advantage of these combinations (Freeman et al 2003, Proulx et al 2003). For patients that have undergone surgery to reduce bulky disease down to microscopic disease, radiotherapy is used in the adjuvant setting. Using a total of 6 fractions (once weekly for 6 weeks or twice weekly for 3 weeks) the 1-year survival rate is 48%, 2-year survival rate 21% and the median disease-free interval (MDFI) 235 days/8 months and the MST 240–363 days (Freeman et al 2003). Palliation of MM (coarse fractions, 4 treatments) gave 69% complete response and 31% partial response (Blackwood & Dobson 1996). Metastasis was the major cause of death, and 58% of patients were euthanized or died of metastatic disease.

For patients with large tumours, where surgery is declined or when there is already evidence of metastatic disease, radiotherapy is a palliative treatment that can reduce tumour burden and improve quality of life. Typically the authors recommend three treatments once weekly when minimal disease is present and four treatments once weekly for palliative treatment. Positive lymph nodes should also be either irradiated or excised as part of a palliative protocol.

Prognosis with chemotherapy

MM is resistant to chemotherapy and there is no known effective chemotherapeutic agent for metastatic MM. A number of approaches using platinum-based drugs have attempted to improve long-term survival in patients with large primary tumours, e.g. intralesional cisplatin. In one study of 20 dogs, intralesional cisplatin gave 70% partial response with implant complications (mild local necrosis) in 85% of patients. MST was 51 weeks for responders (compared with 10 weeks for non-responders) (Kitchell et al 1994). Tumours located on the mandible had a better prognosis than maxillary tumours.

In another study on 27 dogs given carboplatin chemotherapy the response rate was 28%, with 4% complete response, 24% partial response and 36% each with stable disease and progressive disease. Median duration of partial response was 165 days; smaller dogs were more likely to respond but experienced a higher incidence of gastrointestinal side effects (Rassnick et al 2001).

It is in the field of immunotherapy that the next step forward is likely to occur with the development of a tumour vaccine.

MM immunotherapy

It is known that administering bacillus Calmette–Guérin (BCG) or levamisole does not improve survival. There is a mild survival advantage with advanced local disease with surgery and *Corynebacterium parvum* compared with surgery alone (MacEwen et al 1986). Intralesional injection of granulocyte–macrophage colony-stimulating factor (GM-CSF) or interleukin-2 (IL-2) induced partial or complete response and prolonged survival time compared to historical controls (Dow et al 1998).

Surgery and liposome muramyl tripeptide immunotherapy (L-MTP) showed that 80% of patients with stage I disease were still alive at 2 years compared with 25% who underwent surgery alone. L-MTP did not influence survival in patients with stage II or III disease (MacEwen et al 1986). IL-2 and interferon (IFN) induce natural killer (NK) cells, lymphokine-activated killer (LAK) cells and augment antibody-dependent cellular cytotoxicity, and are promising avenues of research because MM is highly immunogenic. Immunotherapy and radiotherapy may be synergistic.

Tumour vaccines

At the time of writing, a tumour vaccine has been given a conditional license by the US Food and Drug Administration for the treatment of canine patients with stage II–IV oral melanoma. The vaccine uses a DNA plasmid containing a human tyrosinase gene. Tyrosinase is present in canine melanoma cells and although similar to the canine tyrosinase the xenogeneic DNA stimulates an immune response against melanoma cells expressing this gene (Bergman et al 2006, Liao et al 2006). Currently the vaccine is recommended for patients that have received appropriate treatment, surgery or radiotherapy for local or regional disease that have an expected survival time of 60–150 days; those receiving the vaccine have been reported to have increased survival times up to 389 days (Bergman et al 2003).

Squamous cell carcinoma (SCC)

SCC accounts for 20–30% of all oral tumours in dogs (second most common after MM) (Cohen et al 1964, Dorn & Priester 1976, Kosovsky et al 1991). The mean age is 8–10 years. No sex or breed predilection has been identified but large breeds may be over-represented. Location within the mouth can be close to the incisors, premolars on the mandible or molars on the maxilla. The tongue and the tonsils are also sites of involvement.

SCC present as irregular, raised, cauliflower-like, ulcerated masses (**Figure 13.3A**). At diagnosis 77% have radiographic evidence of bone involvement (Evans & Shofer 1988, Todoroff & Brody 1979). Evidence of RLN involvement is present in less than 10% of cases at diagnosis, although lymph nodes may be enlarged due to the production of inflammatory cytokines by the tumour. Pulmonary metastasis is present in a small percentage of patients at diagnosis. RLN and pulmonary metastasis are more common with caudal tongue and tonsillar SCC. Papillary SCC in young dogs is

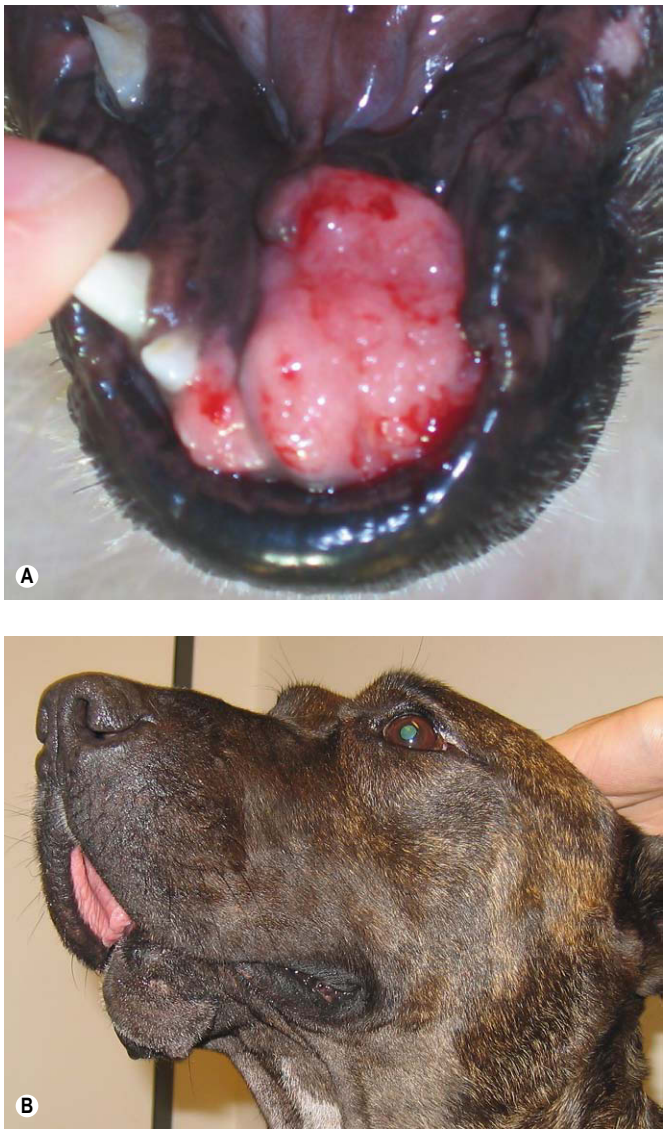


Figure 13.3 (**A**) Mandibular squamous cell carcinoma. (**B**) Post mandibulectomy (different dog).

locally invasive but does not metastasize (Ogilvie et al 1988).

Prognostic factors

SCC of the base of the tongue and the tonsil is highly metastatic (metastasis in up to 73%) and recurs locally or regionally (Beck et al 1986, Brooks et al 1988). Good prognostic factors include rostral location for SCC originating from the gum. Long-term survival and cure is possible for SCC treated with appropriate surgery (not including tonsillar or base of the tongue).

Prognosis with surgery

The prognosis with surgery (particularly mandibulectomy) is good (**Figure 13.3B**). In one study, (Kosovsky et al 1991) the 12-month survival rate was 91% (MST 16–26 months), with only 10% of patients having recurrence. Good results were also reported after maxillectomy (Wallace et al 1992) with 12-month survival rates of 57% (MST 10–19 months) and a higher rate of recurrence (25%).

Prognosis with radiotherapy

For patients where radiotherapy is used only as a palliative option, without prior surgery, response rates were good to fair, with MST of 16 months. Radiotherapy can be used in the adjuvant setting when clean margins have not been achieved and the overall MST is the order of 34 months (LaDue-Miller et al 1996).

Prognosis with chemotherapy

There is no known effective chemotherapeutic agent for primary or metastatic SCC. Piroxicam has been advocated as a treatment option and in one study of 17 dogs resulted in 6% complete response, 11% partial response and 29% with stable disease. Location was not significantly related to response but median progression-free interval was significantly better for responders (180 days) than dogs with stable disease (102 days) (Schmidt et al 2001). Another study on nine dogs given cisplatin and piroxicam had unacceptable renal toxicity (Boria et al 2004).

Tonsillar squamous cell carcinoma (SCC)

Tonsillar SCC has been associated with pollution (10 times more common in urban areas) (Reif & Cohen 1971). Other tumours of the tonsil include LSA and melanoma (metastasis or primary lesion). Distant metastasis (lungs) is found in only 10–20% of cases at the time of presentation but the RLN are highly likely to be affected. Tonsillectomy is rarely curative and should be done bilaterally (due to a high percentage of bilateral disease, even if tonsils are not enlarged) (Todoroff & Brodey 1979).

Radiotherapy gives up to 75% control of local disease, although the prognosis is poor with a 12-month survival rate of less than 10% (Brooks et al 1988, MacMillan et al 1982). Chemotherapy is ineffective although cisplatin and bleomycin have been used with limited success (Brooks et al 1988, Buhles & Theilen 1973). Murphy et al (2006) reported five dogs with tonsillar carcinomas treated with surgical cytoreduction, followed by coarse fractionated radiotherapy together with carboplatin, with an MST of approximately 7 months.

The authors' recommendation is tonsillectomy and radiotherapy (with one treatment at the time of surgery), followed by radiotherapy with carboplatin as a radiation sensitizer and follow-up carboplatin for 2–3 cycles. In a small number of cases MST is 10 months.

Lingual squamous cell carcinoma (SCC)

For SCC of the rostral tongue the prognosis with surgery (partial glossectomy) is fair. Up to 40–60% of the tongue (mobile portion) can be removed and is well tolerated. There may be postoperative dehydration and anorexia, and thermoregulation can be difficult in hot, humid conditions. In the initial postoperative period, some animals may benefit from a feeding tube (e.g. oesophageal, naso-oesophageal) and supportive fluid therapy until able to maintain adequate hydration and nutrition. The MST is 18 months. When surgery is not possible, then radiotherapy as a palliative is indicated (**Figure 13.4**).

Lingual SCC is graded I–III based on degree of differentiation, keratinization, mitotic rate, tissue invasion, vascular invasion, pleomorphism and scirrhous reaction. Prognosis

Figure 13.4 Sublingual squamous cell carcinoma in a dog.

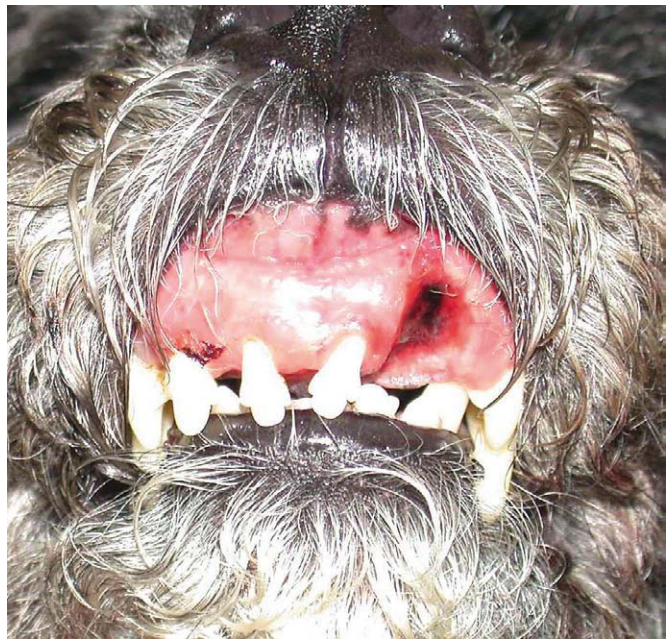


Figure 13.5 HLGBHG sarcoma. (Courtesy R Straw.)

depends on grade and stage of disease. Grade 1 MST is 16 months, Grade 2 MST is 4 months, and Grade 3 MST is 3 months (Carpenter et al 1993). Complete excision with 1 cm margins should be performed.

Prognosis with surgery or radiotherapy

The 12-month survival rate is 50% for complete resection and 60–80% for complete resection with low-grade histology (Carpenter et al 1993). Due to the difficult location, early detection is imperative to allow complete excision.

Radiotherapy can be used in the adjuvant or neoadjuvant setting. Side effects from radiotherapy include fibrosis of the tongue.

Fibrosarcoma (FSA)

This is the third most common oral tumour and accounts for 10–20% of oral tumours (Cohen et al 1964, Dorn & Priester 1976, Todoroff & Brodey 1979). The median age is 8 years and males may be predisposed. The most frequent location is the gingiva, usually on the maxillary arcade between canine and carnassial teeth, hard palate and buccal mucosa. Usually they are flat, firm, multilobulated and deeply attached. They are locally invasive to the gum and bone, and recurrence is common after surgical excision.

Radiographic evidence of bone involvement is seen in 60–65% of patients at the time of diagnosis (Todoroff & Brodey 1979); pulmonary metastasis is present in less than 10%. RLN metastasis is an infrequent finding at diagnosis. The common problem of all sarcomas is local recurrence and oral FSA presents an even greater challenge to the oncologist to establish local control.

Low-grade oral FSA with slow growth should be differentiated from low-grade oral FSA with aggressive biological behaviour (histologically low-grade yet biologically high-grade, or HLGBHG) (Ciekot et al 1994).

High-grade anaplastic oral FSA behaves similarly to HLGBHG with aggressive behaviour, and both have a higher metastatic potential than low-grade FSA with slow growth. Low-grade lesions with slow growth may be more likely to arise from the external surface of the maxilla, whereas HLGBHG occurred in the mandible in 28% of cases in one study (Ciekot et al 1994).

The cornerstone of treatment is surgery (mandibulectomy/maxillectomy). FSAs have a poor response to radiotherapy and chemotherapy (Thrall 1981). Radiotherapy can be used alone or in combination with surgical excision. Radiation in combination with surgery has been shown to be therapeutic. The response rates to chemotherapeutic agents are low and only of short duration (Withrow & MacEwen 2001). Local control is more important than metastatic disease for prognosis, as local recurrence is the most common cause of death.

Dogs with oral FSA treated with surgery alone had a local recurrence rate of 32–57%, with 1-year survival rates of 31–50%, MST of 9.5–11 months, and distant metastasis occurred in 27% (Schwarz et al 1991b, White 1991, Withrow & MacEwen 2001). A combined dorsolateral and intraoral approach for resection of maxillary tumours in 20 dogs achieved clean margins in 70% and a median time to recurrence of 24 months. This approach may prolong survival time for maxillary FSA compared to traditional intraoral techniques (Lascelles et al 2003). Dogs treated with radiotherapy alone achieved a median survival time of 7 months (Thrall 1981). For dogs with large tumours, preoperative radiotherapy to shrink the tumour prior to surgery should be considered.

Histologically low-grade/biologically high-grade (HLGBHG) oral fibrosarcoma (FSA)

HLGBHG oral FSA lesions are characterized by an innocent histological appearance but aggressive biological behaviour (**Figure 13.5**). They are reported to occur predominantly in the maxilla (72%) of large breed dogs, especially Golden Retrievers (54%) (Ciekot et al 1994). Biologically high-grade oral FSAs are often interpreted histologically as fibroma, low-grade FSA, nodular fasciitis, chronic inflammatory nodules or granulation tissue, due to fibroblast proliferation with minimal

cellular aplasia, low mitotic rate, minimal nuclear pleomorphism and abundant production of collagenous matrix. However, histologically aggressive infiltration of surrounding muscle and bone and poor demarcation of adjacent normal tissue are also seen, despite low cellularity. Of 25 dogs, 72% had radiographic evidence of bone lysis (at presentation), 20% had regional lymph node metastasis and 12% had pulmonary metastasis at subsequent examination or necropsy (Ciekot et al 1994).

The prognosis is variable, and depends upon early diagnosis and aggressive treatment. Prolonged survival times can be achieved in some dogs with surgery, radiotherapy alone, surgery and radiotherapy, and radiotherapy and local hyperthermia (Ciekot et al 1994).

Oral undifferentiated malignancy of young dogs

This is a rapidly growing malignancy of young dogs (6–22 months), mostly found in large breeds. Histogenesis is undetermined on biopsies. The fast-growing mass in these dogs most commonly affects the hard palate, upper molar teeth, maxilla and orbit. Many dogs have metastasis. A biopsy shows an undifferentiated malignancy of undetermined histology. In one study, five of six dogs had metastasis beyond head and neck at post-mortem examination (Patnaik et al 1986). No effective treatment has been proposed. Euthanasia within 30 days of diagnosis is common, as these dogs have progressive debilitating disease (Withrow & MacEwen 2001).

Osteosarcoma (OSA)

OSAs account for 11.5% of canine oral tumours (Wallace et al 1992). Mandibular OSA accounts for approximately 27% of all axial OSA (and <4% of all OSA cases) (Heyman et al 1992). They are possibly associated with lower metastatic rate and a more favourable prognosis than appendicular OSA (see Chapter 21).

Multilobular osteochondrosarcoma (MLO)

The mean age for dogs with MLO is 7.5–8 years (Dernell et al 1998, Straw et al 1989). When treated with surgical resection, the MST is 800 days with less than 50% local recurrence and about a 50% metastatic rate (**Figure 13.6**). Adjuvant radiotherapy may be useful for incomplete resection (Straw et al 1989).

Histological grade is a prognostic indicator: Grade 1 MST is 50 months, Grade 2 MST is 22 months, and Grade 3 MST is 11 months (Straw et al 1989).

Lip and cheek tumours

The most common tumours are SCC, FSA, MCT, soft tissue sarcomas (STS) and MM. It is important to maintain the ability to open the mouth, therefore biopsy before planning definitive surgery, because radiation may be applicable before, after or instead of surgery.

Tongue tumours

Canine tongue tumours are uncommon with a possible predisposition in white dogs. SCC accounts for 50% of canine tongue tumours. Other differentials include granular cell myoblastoma, MM, MCT, FSA, adenocarcinoma (salivary duct or ectopic thyroid), HSA and haemangioma, rhabdomyoma and rhabdomyosarcoma. Non-neoplastic lesions include calcinosis circumscripta (cats and dogs) and eosinophilic granuloma (dogs).

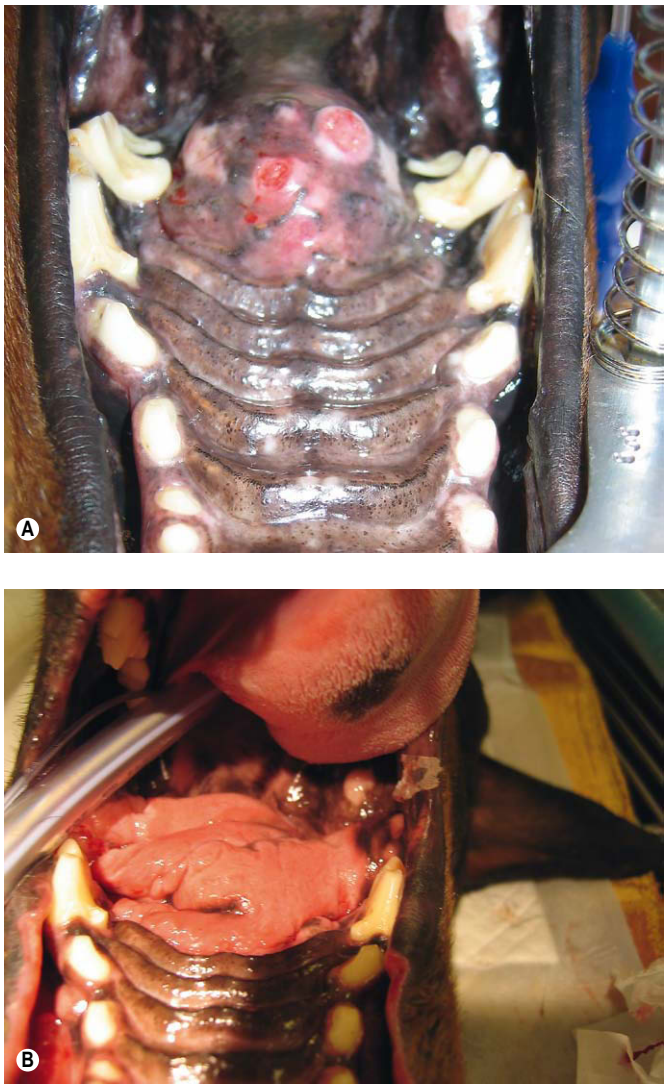


Figure 13.6 Multilobular osteochondrosarcoma. Patient (**A**) before surgery, and (**B**) postoperatively.

The treatment of choice when possible is surgery. For patients not amenable to surgery radiotherapy may be beneficial (SCC, MM, MCT, HSA). Chemotherapy for tumours with known responsiveness may also be beneficial, e.g. MCT. More information on the treatment and prognosis for tongue tumours is discussed under the individual tumour types at the beginning of the chapter.

Odontogenic tumours

Epulides

Epulides are the most common benign oral tumours arising from the periodontal ligament. Fibromatous is the most common (57%), then ossifying (23%), acanthomatous (18%)

and giant cell (2%) (Yoshida et al 1999). Another paper reported 40% acanthomatous, 32% ossifying and 25% fibromatous (Bjorling et al 1987). In this study, the median survival time post-surgery for all oral epulides was 49 months, with a 1-year survival rate of 92%.

Epulides – fibromatous and ossifying

Mean age is 8–9 years and they are seen more frequently in males (Yoshida et al 1999). They are often found on the maxillary premolars as pedunculated masses. Ossifying epulides tend to have a broader base of attachment and be less pedunculated than fibromatous types. They are non-ulcerative, non-invasive, covered by epithelium, do not invade bone and are grossly similar to gingival hyperplasia. Classification of fibromatous or ossifying depends on the histological presence or absence of bone.

Treatment is conservative surgical excision with or without electrocautery. Local tumour recurrence after conservative surgical resection (without bone removal) is 0–17% (Bjorling et al 1987, Bostock & White 1987).

Acanthomatous epulis – basal cell carcinoma

Mean age is 8 years, with no sex predilection and a reported breed predisposition in Shetland Sheepdogs (Yoshida et al 1999). The most common location is around the mandibular canines (60%) and incisors. They are locally invasive, with radiographic bone lysis in 80–90% at diagnosis, but do not metastasize. With wide surgery the prognosis is excellent (Bjorling et al 1987, White & Gorman 1989, Withrow & Holmberg 1983), with only 4% recurrence with appropriate surgery, a 12-month survival rate of 90% and MST of 36 months.

The treatment of choice is dependent on size, location and client preferences; however, wide surgical excision (extending 1 cm beyond the visible or radiographic margin of the tumour) is consistently curative. There is a high incidence of local recurrence after simple excision. Radiotherapy can be used as sole therapy for small lesions (Théon et al 1997b); however, if a complete response is not achieved, follow-up surgery is advised. The authors have used radiotherapy as a means of shrinking very large tumours, and then following with surgical resection.

Prognosis with radiotherapy is good with less than 5% recurrence rate and MST 37 months for small tumours (Thrall 1984). Malignant transformation has been reported in 5–20% of patients and older studies using orthovoltage machines reported bone necrosis in 6% of patients (Thrall 1984). Current day protocols use megavoltage radiation and control rates are good for small tumours; however, the treatment of choice is still surgery.

Intralesional chemotherapy (bleomycin) has been used once weekly for 3–10 treatments on four dogs with recurrent acanthomatous epulis. All (4/4) went into complete remission, with no tumour recurrence for a minimum of 1 year post treatment (Yoshida et al 1998). However, numbers were small.

Epithelial odontogenic tumours (Walsh et al 1987)

These tumours arise from dental lamina and may arise from either dental epithelium or nests of epithelial cells. Odontogenic tumours should be classified according to whether they are of epithelial, mesenchymal or mixed epithelial and mesenchymal origin, rather than based on inductive changes (Gardner 1992).

Inductive fibroameloblastoma

These rare tumours occur in young cats (6–18 months), more frequently in males. They are usually located rostrally, including the canine teeth of the mandible or maxilla (more common). There is a variable degree of bone destruction and proliferation; expansion with deformity of the teeth is common. The treatment is either mandibulectomy/maxillectomy or radiotherapy. Metastasis is not reported (Stebbins et al 1989).

Odontoma

Both rare and benign, these tumours arise from the dental follicle during early stage tooth development. The diagnosis is made when there is evidence of induction of both enamel and dentin. These are intraosseous and locally invasive but do not metastasize. Treatment includes surgical debulking and cryosurgery or wide surgical excision (Figueiredo et al 1974).

Non-inductive epithelial odontogenic tumours

Ameloblastoma and calcifying epithelial odontogenic tumour

Ameloblastoma is often confused with acanthomatous epulis on histology. Ameloblastoma is intraosseous and locally invasive but does not metastasize, and treatment is a wide surgical resection or surgical debulking and radiotherapy. MST following radiotherapy in dogs is 2 years (Langham et al 1977, Dubielzig & Thrall 1982).

Calcifying epithelial odontogenic tumour is a benign and rare tumour of the tooth-forming apparatus and produces a mineralized substance and amyloid. This causes a slow invasion of adjacent tissue resulting in osteolysis or deformation of mandible or maxilla. Treatment is either mandibulectomy or maxillectomy.

Oral tumour-like lesions

- Gingival hyperplasia
- Granulomatous reaction
- Osteomyelitis
- Peripheral giant cell granuloma
- Nasopharyngeal polyp
- Lymphocytic plasmacytic gingivitis-pharyngitis
- Odontogenic keratocyst
- Hamartoma
- Eosinophilic granuloma complex

Viral papillomatosis

The cause is horizontal transmission of papovavirus and usually occurs in young patients and more commonly in dogs (Norris et al 1985). The lesions are wart-like and multiple in the oral cavity, pharynx, tongue or lips. Spontaneous regression can occur in 4–8 weeks. Recommended treatment is surgery, cryosurgery or electrosurgery if severe or interfering with swallowing. Crushing lesions in situ may release antigen and result in immune-induced regression. The prognosis is excellent.

Canine oral eosinophilic granuloma

Seen in young dogs (1–7 years), there is a breed predisposition in Siberian Huskies and Cavalier King Charles Spaniels (Bredal

et al 1996, Madewell et al 1980). These frequently raised, ulcerated lesions on the tongue often spontaneously regress, otherwise corticosteroids or surgical excision is required. Recurrence is rare.

Dentigerous cyst

These cysts arise within islands of odontogenic epithelium (**Figure 13.7**). They are benign, non-neoplastic circumscribed cystic lesions that may represent an early stage of a continuum to malignant epithelial tumours, e.g. basosquamous carcinoma (Poulet et al 1992). They are seen as closed cavities or cysts, with one or more teeth embedded in the cyst wall (Baxter 2004). Diagnosis is by radiographs with a characteristic radiolucent halo around a non-erupted tooth originating at the cemento-enamel junction and enveloping the crown of the tooth. Treatment of choice is surgical removal of the non-erupted tooth and cyst lining. Thorough curettage of the walls of the cyst is required to prevent recurrence.

Salivary gland tumours

These are rare in dogs. Mean age of affected dogs is greater than 10 years. No consistent breed predisposition has been reported (Hammer et al 2001). Mandibular and parotid glands are the most frequently involved (Carberry et al 1987). Although most are malignant (adenocarcinomas), benign lesions do occur (adenoma and lipoma) (Brown et al 1997, Stubbs et al 1996). Other malignant histological types include SCC, MCT, etc. Sialadenitis, sialoceles and salivary gland abscesses are differential diagnoses. Metastasis to RLN, lung, bone, eyes and kidneys has been reported (Grevel et al 1978, Habin & Else 1995).

Fine needle aspiration (FNA) cytology and biopsy are important for diagnosis (incisional biopsy prior to definitive surgery). The RLN should be palpated and assessed by FNA, or biopsy if enlarged. Thoracic radiographs/CT should be taken as part of staging. CT/MRI scans of local tumour may be of use to plan definitive surgical resection ± radiotherapy. Removal of the tumour with wide margins may be difficult due to location; however, a unilateral vagosympathetic trunk, jugular vein and carotid artery may be sacrificed with minimal morbidity in the dog. The surgeon should be familiar with normal regional anatomy of this area.

Radiation and chemotherapy may be used adjuvantly to surgery. This may improve survival times over surgery alone; however, detailed reports of survival outcomes comparing these groups are not available due to the small number of cases.

The authors suggest that dogs with non-metastatic disease have a better prognosis when treated with surgery than cats, as wider margins are easier to achieve in dogs. For large fixed tumours, radiotherapy can be utilized to shrink the tumour.

Histopathological features were not found to be prognostic in one study (Hammer et al 2001), although clinical stage was predictive.

Nasal tumours

Nasal planum tumours

These tumours are rare in dogs and by far the most common is SCC. SCC has been correlated with ultraviolet light and lack of protective pigment. Depending on the timing of the biopsy, SCC is often slowly progressive from carcinoma in situ to superficial SCC to deeply infiltrative SCC. Other cancers reported in this site are LSA, FSA, haemangioma, MM, MCT, fibroma and histiocytoma. Immune-mediated disease may present as erosive or crusty lesions on the nose but these are rarely proliferative, and usually other sites on the body are affected. Immune-mediated disease is probably not a contributing factor in tumour development.

History and clinical signs

Invasive SCC is usually preceded by a protracted course of disease (months to years) that progresses through stages. First there is crusting and erythema, then superficial erosions and ulcers (typically carcinoma in situ or early SCC) and, finally, deeply invasive and erosive lesions (**Figure 13.8**). Because SCC has a low rate of metastasis, which, if it occurs, does so late in the course of disease, dogs can have prolonged survival even if left untreated, although there is unacceptable morbid-

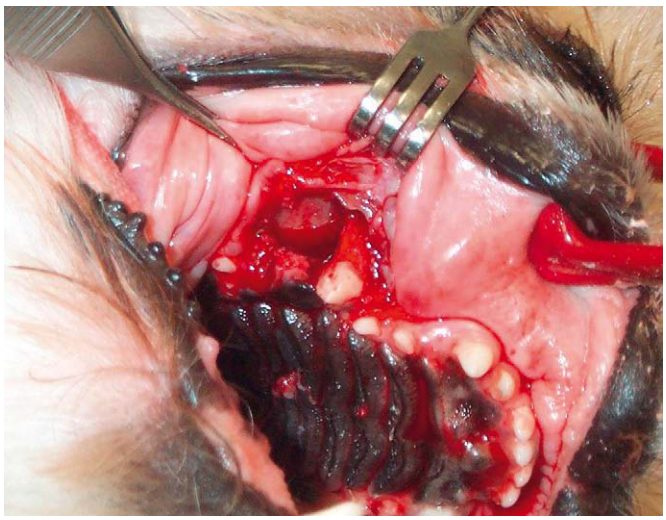


Figure 13.7 Dentigerous cyst.

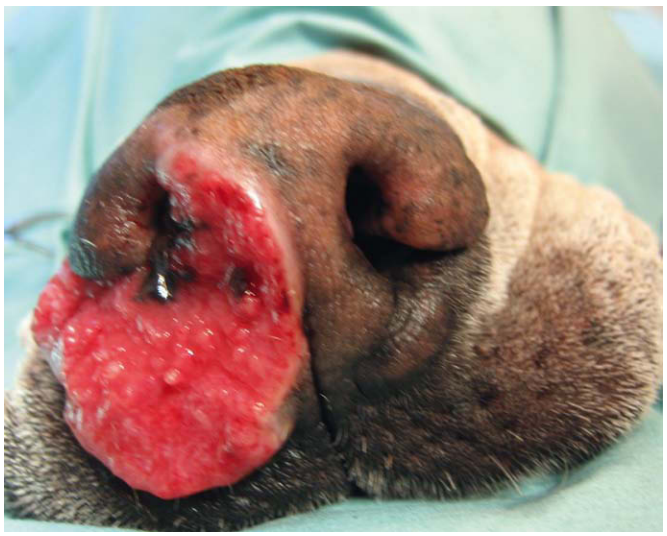


Figure 13.8 Nasal squamous cell carcinoma.

ity associated with an ulcerated, invasive, deforming and secondarily infected cancer.

Diagnostic work-up

Erosive or proliferative lesions should be biopsied (wedge). Care should be taken not to compromise a definitive surgical procedure (i.e. nasal planectomy).

Cytology and superficial biopsies are not useful. Lymph nodes are usually negative except with advanced disease and thoracic radiographs are invariably negative for metastases. Regional radiographs are generally unrewarding. CT/MRI are valuable for staging dogs with SCC of the nostril to help define the posterior extent of disease and hence level of resection. Rhinoscopy can also assist in determining the extent of caudal disease and to look for multiple lesions in dogs (Banks & Straw 2004).

Treatment

It may be possible to prevent or arrest the course of preneoplastic disease by limiting exposure to sun or tattooing to add pigment protection. Topical sunscreens are readily licked off and rarely help.

When inflammation and ulceration are present it is very difficult to maintain the tattoo as it is rapidly removed by macrophages. At best, tattoos would need to be repeated regularly.

Attempts to increase epithelial differentiation with synthetic derivatives of vitamin A are generally unsuccessful for advanced disease, but may be helpful in reversing or limiting the growth of preneoplastic lesions.

SCC can be divided into two categories depending on the degree of invasiveness:

1. *Superficial, minimally invasive disease* (can be treated effectively with cryosurgery, lasers, photodynamic therapy, intralesional carboplatin, hyperthermia or irradiation)
2. *Deeply infiltrative disease*.

In the authors' experience, Golden Retrievers are overrepresented with infiltrative SCC. If large, these tumours are difficult to control. The nasal planum should be completely removed with the tumour, if possible with margins of 1 cm of grossly normal tissue. If the margins are incomplete, adjuvant radiotherapy has been successful, resulting in a cure in one of four dogs (25%); however, the other three dogs had local recurrence at a median of 9 weeks (Lascelles et al 2000). Combined removal of premaxilla and nasal planum has been reported in the dog, with acceptable cosmetic appearance, good function and tumour control (Kirpensteijn et al 1994). An improved cosmetic appearance is reported with the use of bilateral labial mucocutaneous rotation-advancement flaps after nasal planectomy and premaxillectomy for SCC in the dog (Gallegos et al 2007). Another paper describes aggressive rostral maxillectomy and nasal planectomy. Complete margins were obtained in all cases, but one dog had local recurrence 10 months after surgery. All others had no signs of local recurrence during an 11–66 month follow-up period (Lascelles et al 2004) (**Figure 13.9A,B**).

Combined systemic chemotherapy and then surgery have been used in one dog to reduce tumour size, allowing it to be more amenable to wide surgical resection (Banks & Straw 2004); however, radiotherapy is more likely to be successful in the neoadjuvant setting. Surgical resection of the nasal planum with clean margins correlates to prolonged survival and potential cure (Gallegos et al 2007, Kirpensteijn et al 1994, Lascelles et al 2000). One potential problem in the months following surgery is stricture of the combined nasal orifice, and attempts at managing this in dogs include wide skin excision and removal of the nasal septum rostrally, laser ablation, rubber stents or permanent placement of a stainless steel intraluminal expansile stent.

Radiotherapy is applicable in the management of deeply infiltrative tumours as palliative therapy in patients where surgery is declined or when disease is very extensive; survival times range from 8 weeks to greater than 1 year. For early disease, excisional biopsy and radiotherapy is an option with good cosmesis and long-term control (**Figure 13.9C**).

Prognosis

The prognosis is good for early, non-invasive disease. Later stage disease can be cured with aggressive surgery (**Figure 13.9**), but is poorly responsive to most other treatments.

Later development of new sites of neoplasia on other areas of planum is common, because the underlying cause (the cumulative toxic effect of previous exposure to UV radiation) is not reversible.

The local recurrence rate in dogs after nasal planectomy is low. Delayed (greater than 1 year) lymph node metastasis in dogs with SCC has been successfully treated with lymphadenectomy (Withrow 2007).

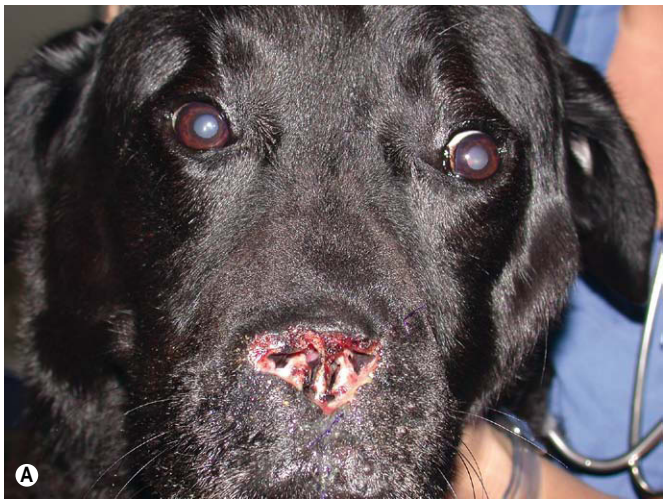
Many clients will decline radical surgery, based on cosmesis, and therefore minimal surgery and radiotherapy is an option. This option is only applicable for early disease. In patients with more extensive disease, where surgery is declined, radiotherapy as a palliative treatment is an option. The best long-term prognosis is for patients where early diagnosis and treatment is performed.

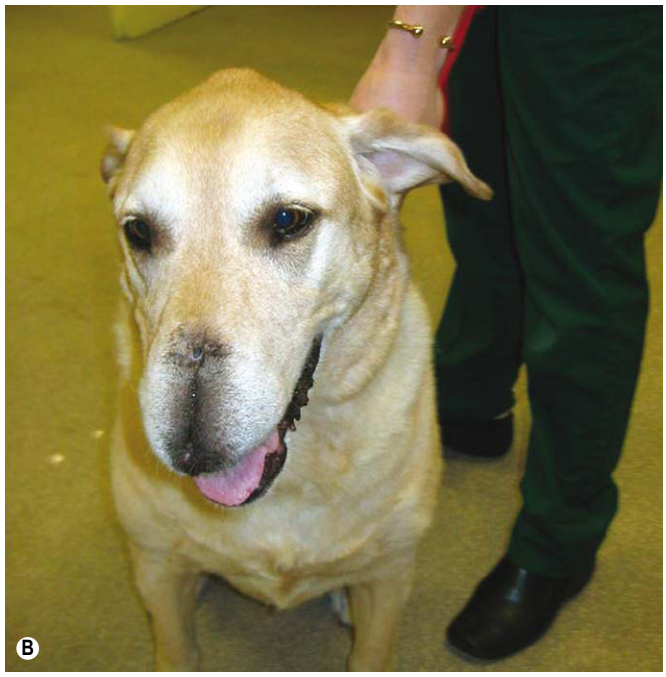
Nasal cavity tumours

Intranasal cancer accounts for 1% of all canine neoplasms (MacEwen et al 1977). It is speculated but unproven that doliocephalic breeds living in urban environments with resultant filtering of pollutants may be at a higher risk for developing nasal cancer. Exposure to environmental tobacco smoke has been associated with an increased risk of nasal cancer in a group of dogs in one study (Reif et al 1998), but not in another. The average age of affected dogs is 10 years (Patnaik et al 1984). Medium to large doliocephalic breeds and male dogs may be more commonly affected. Chondrosarcoma (CSA) has been shown to occur in younger dogs (**Figure 13.10**).

Two-thirds of nasal cavity tumours are carcinomas (adenocarcinoma, SCC, undifferentiated carcinoma) (Madewell et al 1976). Other tumours include sarcomas (FSA, CSA, OSA and undifferentiated sarcomas) as well as LSA, MCT and HSA (Patnaik et al 1984). All are locally invasive. The metastatic rate is low, and if metastasis develops the regional lymph nodes and lung are the most common sites (Patnaik 1989, Patnaik et al 1984).

Rarely, transmissible venereal tumour (TVT) and polyps/fibromas will be seen.





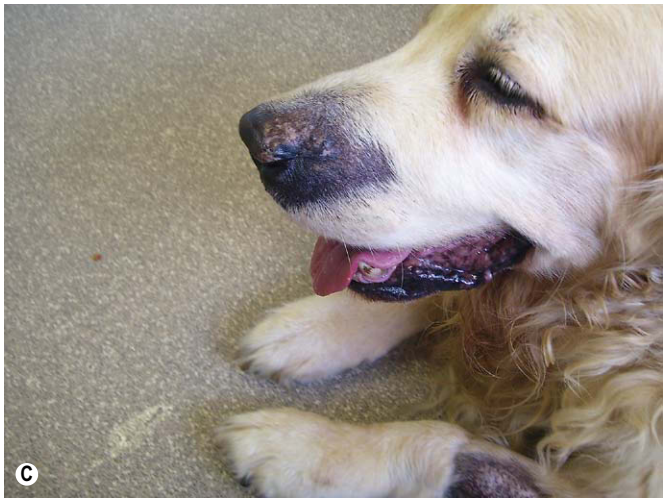


Figure 13.9 (**A, B**) Dogs after nasal planectomy. (**C**) Dog after cytoreductive surgery and radiation.

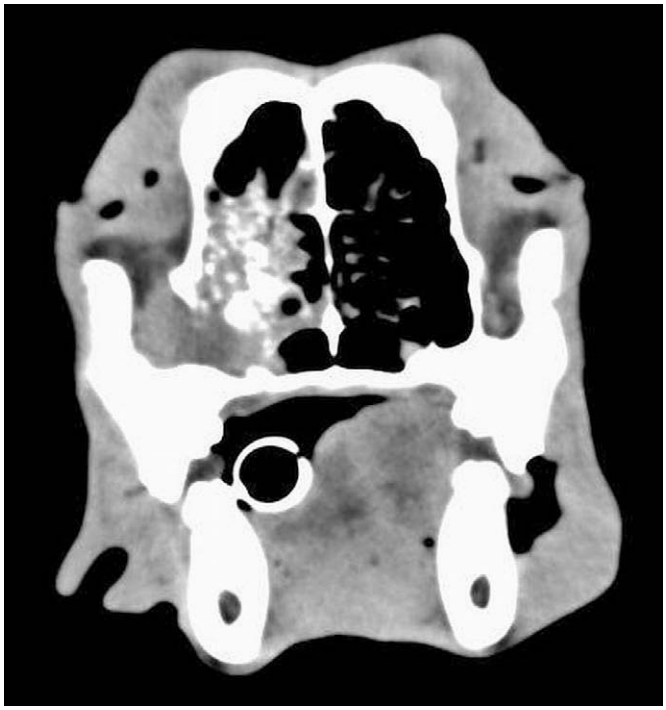


Figure 13.10 CT of a young dog with nasal chondrosarcoma.

Other differential diagnoses include hypertension, bleeding disorders, fungal (Aspergillus, pythiosis) or infectious rhinitis, developmental abnormalities like cystic Rathke's clefts, nasal foreign bodies, salivary mucocele, cystic polypoid lesions of nasal turbinates, folds of redundant mucosa, and nasopharyngeal stenosis.

History and clinical signs

In patients that present with a history of intermittent and progressive unilateral epistaxis and/or mucopurulent nasal discharge, facial swelling or epiphora, the most probable diagnosis is neoplasia. Average duration of clinical signs is 3 months (MacEwen et al 1977). If facial deformity and to a lesser degree epiphora are present, the diagnosis is almost always cancer. A partial or short-term response to a variety of symptomatic treatments is commonly seen. Uncommonly, dogs will present with neurological signs due to direct invasion of the cranial vault by tumour. It is important that any patient with a unilateral nasal discharge or epistaxis undergoes full diagnostic work-up. The secret to prolonging survival times in these patients is early diagnosis!

Diagnostic work-up

A definitive diagnosis requires a tissue biopsy, even though radiographs and history can be very suggestive. Rule out sys-

temic bleeding disorders prior to CT scan/radiographs and biopsy. Pay attention to platelet count, clotting profile and clinical signs of a coagulopathy, such as bleeding from venopuncture sites, haematuria, petechial haemorrhages, etc.

A CT/MRI scan is the imaging tool of choice in all cases where a nasal tumour is suspected (**Figure 13.11**). A CT scan is required computer planning for radiotherapy.

In cases where CT/MRI (especially CT) is not available, radiographs can be used. The standard work-up would include lateral, DV, frontal sinus, open mouth and oblique views. Asymmetric destruction of turbinates and superimposition of a soft tissue mass over the turbinates, especially in the caudal half of the nose, are classic signs of neoplasia. Bone destruction or erosion is also common. Fluid in one or both frontal sinuses without bony erosion is usually secondary to outflow obstruction from the sinus. CT is ideal to assess cribriform plate and orbital invasion.

Rhinoscopy provides no information regarding bone lysis (Saunders et al 2003) but can be used if CT/MRI is suggestive of fungal rhinitis, to visualize fungal colonies. Rhinoscopy is valuable to visualize a mass lesion prior to biopsy. Rhinoscopy and CT/MRI can be used to locate the best region for a representative tissue biopsy. The samples collected via rhinoscopy-assisted punch biopsy will be small, superficial and erroneous in at least 17% of cases (Lent & Hawkins 1992). Vigorous nasal flushes may be diagnostic if able to dislodge pieces of tumour, but samples are generally inadequate (MacEwen et al 1977). Transnostril core biopsy using a large bore plastic cannula and syringe retrieves an adequate tissue sample in most cases (Withrow et al 1985), as does transnostril biopsy using alligator rongeur forceps (either of these techniques are the authors' preference). Care should be taken not to penetrate the cribriform plate (no samples taken further caudally than the medial canthus of the eye). Mild to moderate haemorrhage is to be expected (generally will subside within a few minutes; if severe, ipsilateral carotid artery can be ligated permanently), severe haemorrhage can be seen if the tumour is HSA. Sedation and overnight hospitalization may be required in rare cases if bleeding is persistent. Obtaining a definitive diagnosis can be frustrating due to secondary rhinitis and haemorrhage. In some unusual cases a rhinotomy is required for diagnosis. Other instruments for transnostril biopsy include a bone curette.

Figure 13.11 Advanced nasal carcinoma.

Lymph node aspirates are rarely positive, but are most likely to be so with poorly differentiated carcinomas and thoracic radiographs are usually normal. If any CNS signs are present, it is essential to have a CT/MRI scan before proceeding with treatment.

Treatment

Local disease control is the aim of therapy. Unfortunately, the majority of nasal tumours present at a clinically advanced stage, with tumour extension near the brain and/or eyes not uncommon. With bone invasion occurring early, and most animals presenting with advanced disease, curative surgery is near unattainable. Dogs with untreated, histologically confirmed nasal carcinomas had an MST of 95 days, dogs with epistaxis had an MST of 88 days, and those without epistaxis an MST of 224 days (Rassnick et al 2006).

Surgery

Surgical removal (via rhinotomy) as a single treatment option has a high rate of acute and chronic morbidity without significant extension of life, and so is very rarely indicated. Laing & Binnington (1988) reported 15 dogs with surgically treated nasal tumours. The MST was 9 months, 11 months if the tumour was unilateral and 3 months if bilateral. Surgical treatment (transnasal curettage or rhinotomy) had no survival advantage (Henry et al 1998).

Unilateral or bilateral carotid artery ligation can palliate symptoms of epistaxis for up to 3 months or longer without damage to the brain (in a small number of cases).

Radiotherapy

Radiotherapy is the treatment of choice for nasal tumours.

A number of protocols are reported, including hypo- and fine-fractionated protocols. Overall MSTs for radiotherapy range from 8 to 14 months, irrespective of histological diagnosis (Adams et al 1987, 1998, LaDue et al 1999, Northrup et al 2001, Théon et al 1993).

Rhinitis and mucositis as a result of radiation can be severe, but usually subside within 1–2 months. Patients may need their nose cleaning several times a day, and rarely does the patient have a normal nasal cavity. Ocular changes are expected if one or both eyes receive radiation to 40 Gy in 3 weeks. Keratoconjunctivitis sicca (KCS) is very common, and corneal ulcers and cataracts often occur at doses over 40 Gy.

Intracavitary radiation using radioactive isotopes (brachytherapy) has been explored in a limited number of patients, but problems with dose distribution, isolation of the patient during treatment and radiation exposure to personnel have limited its application. It is not known if it improves survival over external beam radiation.

Combination surgery and radiotherapy

Surgical debulking prior to radiation is non-beneficial due to extent of disease. It not only delays the start of radiotherapy, it also increases morbidity experienced by the patient (Adams et al 1987, Théon et al 1993, Yoon et al 2008).

However, surgical exenteration following accelerated radiotherapy (if tumour is still present on CT) showed significant prolongation of survival times over radiotherapy alone (Adams et al 2005). The overall median survival time for dogs in the radiotherapy plus surgery group was 477 months, compared to 19.7 months for dogs in the radiotherapy-only group. Exenteration after radiotherapy may increase the

risk of chronic complications (rhinitis and osteomyelitis/osteonecrosis).

Immunotherapy and cryosurgery are not recommended in the management of nasal tumours as they have not been shown to improve survival times.

Chemotherapy

Cisplatin has been shown to benefit some dogs (27% response rate) with nasal adenocarcinoma, but MST is only 20 weeks and infinitely inferior to radiotherapy (Hahn et al 1992).

The combination of cisplatin (a known radiation sensitizer) and radiation has been shown in one study to improve survival (median 474–580 days) (Lana et al 1997), but not in other studies. Similar studies using carboplatin revealed no statistical improvement in survival time over radiotherapy alone (Nadeau et al 2004).

A small number of dogs, with various histological types of advanced nasal tumour, were treated with alternating doses of doxorubicin, carboplatin and piroxicam. Six of eight dogs (75%) showed a clinical response. Clinical signs in all dogs resolved after one or two doses and the protocol was well tolerated (Langova et al 2004).

Prognosis

In the absence of radiotherapy prognosis is poor; mean survival for surgery, chemotherapy or no treatment is 3–6 months. Most dogs die or are euthanized as a result of local disease progression (Hahn et al 1992, Henry et al 1998, Withrow 1982).

Consistent improvements for survival have been made with radiotherapy, and the move from orthovoltage to megavoltage radiation, with earlier diagnostics and better treatment planning, should continue to improve overall survival times. One-year survival times ranged from 20 to 82% and 2-year survival times ranged from 10 to 48% (Adams et al 1987, Lana et al 1997, Théon et al 1993). Prognosis for sarcomas, especially CSAs, is better than for carcinomas, and adenocarcinomas respond better than SCC or undifferentiated carcinoma. Few dogs are cured if followed to autopsy, where 40% have metastasis beyond local site (usually lymph node and lung) (Patnaik 1989).

Tumours of the frontal sinus

These are rare tumours, of which the majority are SCC (Rogers et al 1996). Presenting signs are usually the presence of a small hard lump over the frontal sinus. Unfortunately, these tumours are usually advanced on diagnosis and the only treatment option is palliative radiotherapy (**Figure 13.12**). When the tumour is detected early, survival excision and adjuvant radiotherapy is the treatment of choice (**Figure 13.13**). To improve overall survival times, early diagnosis is essential.

Ear tumours

Benign tumours include inflammatory polyps, papillomas, basal cell tumours and ceruminous gland adenomas. The mean age is 9 years, with Cocker Spaniels over-represented, probably because of chronic inflammation of the ear canal, which leads to increased glandular hyperplasia, a precursor to tumour development.

In one paper, 60% of canine ear tumours were malignant and 40% were benign (London et al 1996).

Malignant tumours are seen in slightly older dogs, mean age 10 years, and include ceruminous gland adenocarcinomas, SCC and other cutaneous tumours. They tend to be locally invasive with low rates of metastasis (10% to regional lymph node and lung). Neurological signs are present in 10% of cases. Malignant tumours are usually broad based, with ulceration and haemorrhage; 25% have bulla involvement. Malignant ear tumours appear to be less aggressive in dogs than in cats (London et al 1996). Diagnostic work-up

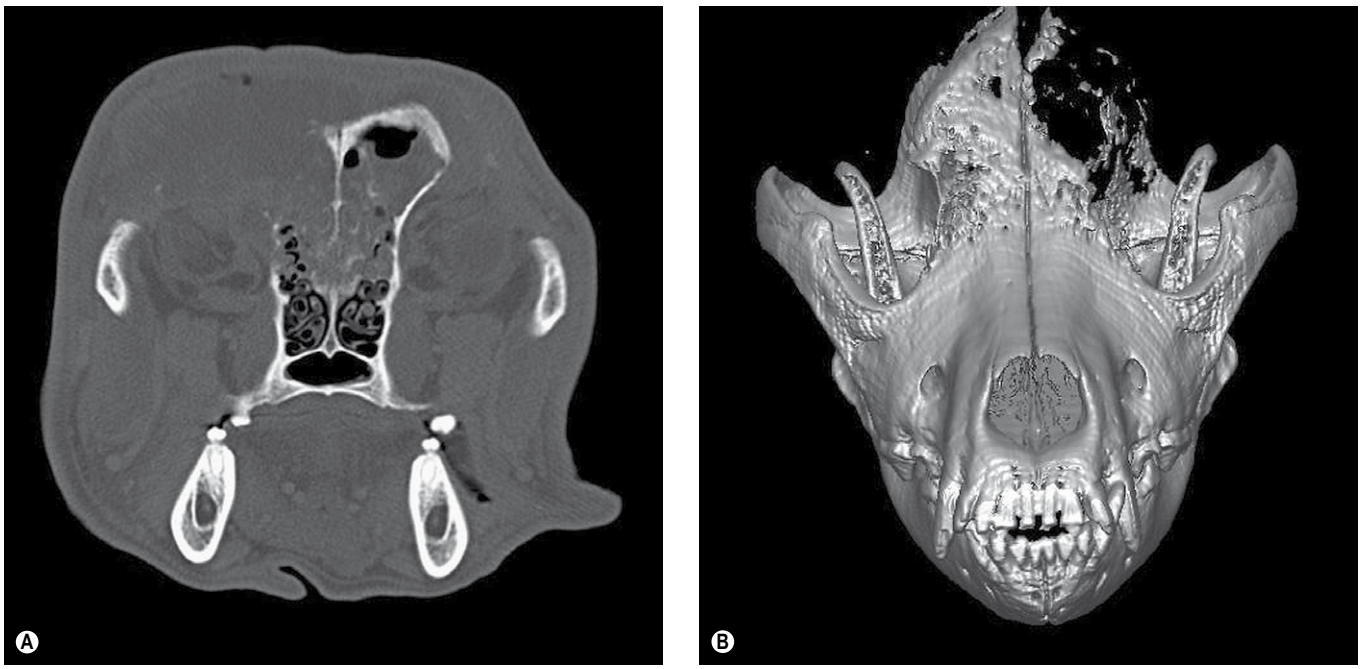


Figure 13.12 (**A**) CT of advanced squamous cell carcinoma of frontal sinus. (**B**) 3-D reconstruction.

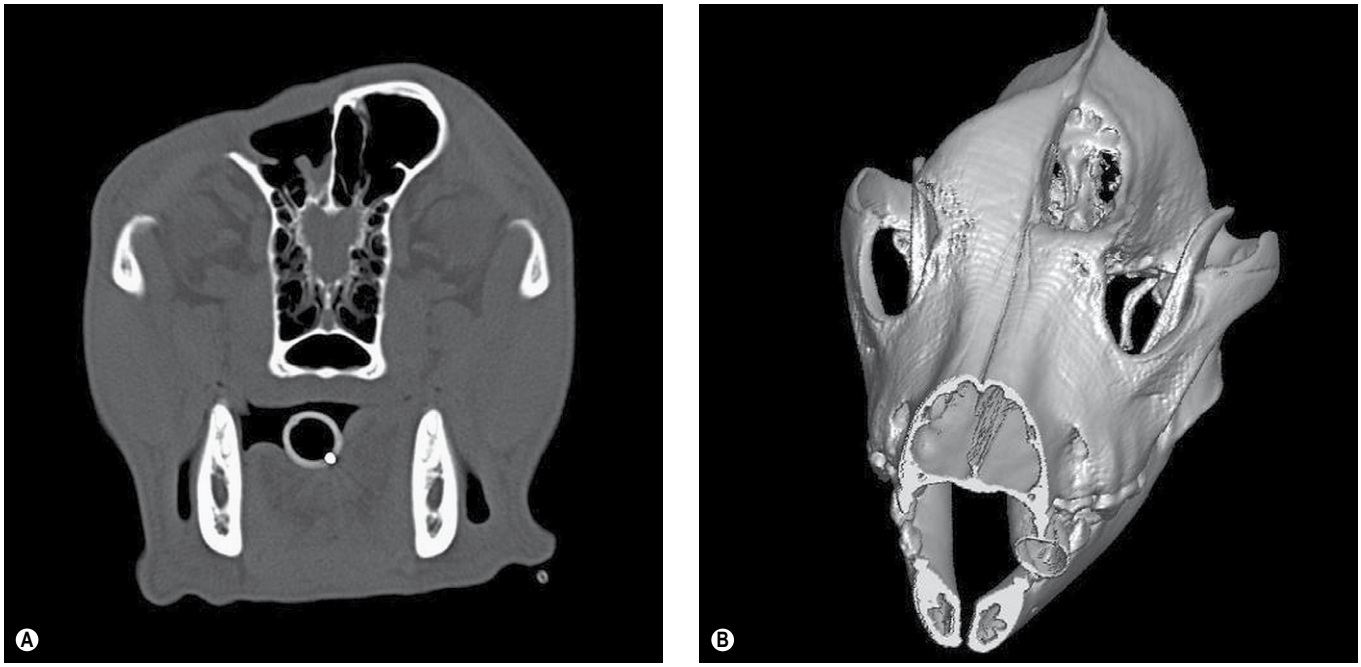


Figure 13.13 (**A**) CT of squamous cell carcinoma of frontal sinus treated with surgery and radiotherapy. (**B**) 3-D reconstruction.

includes otoscopic evaluation, radiographs, CT scan and tissue biopsy.

Treatment and prognosis

The treatment of choice for malignant ear tumours in dogs is surgical resection with clean margins, which requires total ear canal ablation (TECA) and lateral bulla osteotomy (LBO) (London et al 1996, Marino et al 1993). Readers should refer to surgical texts for descriptions of the TECA–LBO surgical technique and possible surgical complications. Conservative surgery is only appropriate for benign tumours.

Poor prognostic factors include invasion of the bulla, extensive tumour and conservative surgery. The MST was 36 months with a 0% local recurrence rate for dogs with malignant ear tumours treated with TECA–LBO. This reduced to an MST of 9 months with a 75% local recurrence rate for conservative surgical resection (lateral wall resection). The MST was only 5.3 months for tumours with extensive involvement, and SCC may be more aggressive than adenocarcinoma (London et al 1996).

Incompletely excised ceruminous gland carcinomas in dogs benefited from adjuvant radiotherapy; however, results were not as favourable as those obtained with appropriate (aggressive) surgical resection with clean margins. In 11 cases of dogs and cats with incompletely resected ceruminous gland carcinomas treated with adjuvant radiotherapy, although the median progression-free survival time was 39.5 months, tumour recurrence was observed in 36% and metastasis in 27% (Théon et al 1994a).

Miscellaneous ear problems

As mentioned above, benign ear tumours can be managed with conservative surgical resection. There is one report in the literature of removal of a cholesteatoma using a caudal auricular approach (Davidson et al 1997). Cholesteatomas are an abnormal growth of epithelium in the middle ear; they are not a granuloma, neoplasm or contain fat. The authors used a caudal auricular approach to the bulla to preserve cosmesis and enable prosthetic reconstruction of the auditory ossicles and facial grafting of the tympanic membrane. The procedure requires an operating microscope.

Inflammatory polyps of the middle ear have been reported in five dogs (Pratschke 2003). The most common clinical signs were otitis media and externa, with radiographic evidence of otitis media. Surgical removal (TECA and LBO or ventral bulla osteotomy) resulted in a good outcome, with no recurrence for a 9–69 month follow-up.

FELINE TUMOURS

Oral tumours

Oral tumours account for approximately 10% of all feline tumours and approximately 90% are malignant (Stebbins et al 1989). They commonly arise from the gingiva or tongue.

Clinical signs

These include changes in facial symmetry, ptyalism, anorexia, sneezing, nasal discharge, pawing at the mouth, changed eating habits, oral hypersensitivity, loose teeth, dysphagia, weight loss or halitosis.

Squamous cell carcinoma (SCC)

This is the most common feline oral tumour (60–70%) (Stebbins et al 1989), typically seen in older cats, median age 15 years (Bregazzi et al 2001). The risk of feline oral SCC increases with the use of flea collars, a higher intake of canned

food (particularly tuna) compared to cats eating mostly dry food, and exposure to environmental tobacco smoke (Bertone et al 2003). Usual tumour sites are mandible, maxilla, sublingual and tonsillar. For tumours of the mandible and maxilla, bone involvement is typical and often extensive, and perineural infiltration by mandibular SCC may be responsible for tumour extension into the retrobulbar space.

RLN and distant metastasis is rare but local tumour control is poor and the long-term course is unknown as most patients are euthanized due to progressive primary disease. Patients may present with enlarged regional lymph nodes, but these are usually hyperplastic due to the production of inflammatory cytokines. Paraneoplastic hypercalcaemia has been reported (Hutson et al 1992). The overall prognosis for oral SCC in the cat is poor. Cats with SCC had significantly shorter survival than cats with FSA or OSA (Northrup et al 2006).

Unfortunately, SCC is advanced before it is diagnosed, making surgery difficult. For small tumours of the mandible and maxilla, surgical excision with margins is the treatment of choice. Hemimandibulectomies can be performed in cats, but in general they do not tolerate surgery as well as canine patients and may require more supportive care including a feeding tube after surgery (Northrup et al 2006). Cats with mandibular SCC treated with mandibulectomy as sole treatment had a median disease-free interval of 340 days, with rostral tumours having an MST of 911 days. Unfortunately, surgical resection of small tumours with clean margins applies to only a few patients.

Prognosis with radiotherapy

Palliative therapy using a variety of radiation protocols ± chemotherapy has been reported (Fidel et al 2007, Posterino et al 1993). The results overall are disappointing, with survival times not significantly better than with no treatment. Most recently, Fidel et al (2007) reported on nine cats treated with accelerated radiotherapy (14 fractions of 3.5 Gy in 9 days) that had a median overall survival of 86 ± 110 days. In another study, eight cats with non-resectable oral SCC treated with low-dose gemcitabine (as a radiosensitizer) and palliative radiotherapy had a median duration of remission of 42 days and a median survival time of 111 days (Jones et al 2003).

Currently, the authors do not advise radiotherapy for SCC except in patients where a good surgical resection has been possible and radiotherapy is for 'clean up' of margins only. Seven cats treated with combination of mandibulectomy and radiotherapy had a 14-month MST (Hutson et al 1992).

Prognosis with chemotherapy

There is no known effective chemotherapeutic agent for primary or metastatic SCC. Mitoxantrone, carboplatin, doxorubicin, cyclophosphamide and gemcitabine have been used either alone or with radiotherapy to some effect (Jones et al 2003). The Cox inhibitors piroxicam and meloxicam have been used, again with no significant improvement in survival times, although meloxicam is considered to improve quality of life for these patients.

DiBernardi et al (2007) determined the Cox-2 expression in feline SCC; 6 out of 34 cats had high intensity staining, whilst 22 out of 34 had weak staining. This would indicate that although the Cox inhibitors may be of benefit to some patients, further evaluation of patient response needs to be tabulated with histopathological data. Fifty-four cats with oral SCC treated in general practices in the UK had an overall MST of 44 days (Hayes et al 2007). Variables associated with survival included cat pedigree, treatment with a non-steroidal anti-inflammatory drug (NSAIDs) and Cox-1 staining distribution.

Oral SCC in the cat is the antithesis of the condition in the dog and the most important prognostic indicator is early detection whilst they may still be surgical candidates.

Fibrosarcoma (FSA)

FSA is the second most common feline tumour with a frequency of 13–20% and a mean age of 10 years (Stebbins et al 1989). These tumours are locally invasive into gingiva and bone and recurrence after surgery is common. RLN metastasis is rare and distant metastasis is seen in approximately 20% of patients as a late event.

Prognosis

Local control is more important than metastatic disease, with local recurrence or poor response to palliative treatment the most common cause of death.

Treatment

Surgery

The treatment of choice, where possible, is surgery, i.e. mandibulectomy or maxillectomy depending on the location. However, as wide surgical margins are required, many patients are not surgical candidates. Mandibulectomy for oral FSA in five cats resulted in a median disease-free interval of 859 days (NC Northrup, personal communication, 2002).

Radiotherapy

These tumours are radioresistant but radiotherapy can be considered as palliative therapy for inoperable tumours. Chemotherapy is unlikely to be beneficial. Again, early diagnosis may help to improve survival times, but overall the prognosis remains poor.

Fibroma

Occurs usually on lips and surrounding facial areas of cats and they respond well to local resection.

Odontogenic tumours

Epulides

Epulides are the most common benign oral tumours arising from the periodontal ligament. Fibromatous epulides accounted for about 8% of feline oral tumours in one study (Stebbins et al 1989). For more information, see canine odontogenic tumours above.

Epithelial odontogenic tumours

These arise from dental lamina and may arise from either dental epithelium or nests of epithelial cells. They account for 2.4% of feline oral tumours. Inductive fibroameloblastomas are rare tumours, producing a variable degree of bone destruction, and deformity of the teeth is common. Treatment includes mandibulectomy/maxillectomy, surgical debulking, cryosurgery or radiotherapy. Good control rates are achieved

with aggressive treatment. Adjunctive radiotherapy is used with good results in cats with incompletely excised tumours.

Viral papillomatosis

The cause is horizontal transmission of papovavirus and is usually seen in young patients. It is more common in dogs but has been reported in cats (Sundberg et al 2000).

Feline oral eosinophilic granuloma

Average age of affected cats is 3.5 years. Females may be predisposed (MacEwen & Hess 1987, Merchant 1994, Song 1994). The cause is unknown; however, an underlying hypersensitivity such as a food allergy, atopy or insect allergy (particularly to fleas and mosquitoes) has often been associated with these lesions (Medleau & Hnilica 2001, Song 1994). Lesions are seen most commonly on the upper lip near the midline but can be anywhere. Lesions are slowly progressive over months to years, causing lip erosion. Biopsy is required to differentiate from oral cancer.

Lesions often improve to some extent with antibiotics, which may be due to an immunomodulatory effect. Immunosuppressive therapy using oral prednisolone (Merchant 1994), subcutaneous injections of methylprednisolone acetate (Medleau & Hnilica 2001, Song 1994), oral ciclosporin (Vercelli et al 2006) and oral dexamethasone or triamcinolone have been used with success. When lesions have improved, glucocorticoid therapy is tapered to the lowest possible dose.

Dietary supplementation with omega-3 and -6 fatty acids has helped some cats. Immunomodulatory drugs can be tried if immunosuppressive therapy fails (e.g. chlorambucil, levamisole, thiabendazole and IFN-α). Radiotherapy, cryosurgery, laser therapy, surgical excision and hypoallergenic diets have also been tried. Megestrol acetate is not recommended due to adverse side effects.

In cats less than 1 year of age, eosinophilic granulomas may regress spontaneously over a period of 3–5 months (Medleau & Hnilica 2001). The overall prognosis is fair for complete and permanent recovery.

Hamartoma

A hamartoma is a non-neoplastic congenital mass of disorganized but mature cells. Seen in younger animals, it seldom recurs following conservative excision and is usually self-limiting. Paraneoplastic hyperglycaemia has been reported in a kitten with a gingival vascular hamartoma.

Tongue tumours

The most common tumour of the tongue is SCC on the ventral surface near the frenulum. The prognosis is guarded, as these tumours are usually too large for surgical intervention (**Figure 13.14**). Radiotherapy has been used as a palliative therapy but overall the results have not been good. Meloxicam can be used to improve quality of life. For more information, see oral tumours SCC.

Salivary gland tumours

In cats, these tumours are usually more advanced at the time of diagnosis than in dogs. Mean age of affected cats is more than 10 years. Siamese cats are reported to be at an increased risk (Hammer et al 2001).

The majority are malignant (adenocarcinomas). Other malignant histological types include SCC, MCT, etc. Sialadenitis, sialoceles and salivary gland abscesses are differential diagnoses. Metastasis to RLN, lung, bone, eyes and kidneys are reported. They are usually unilateral but one cat with a bilateral salivary carcinoma and multiple metastases has been reported (Mazullo et al 2005).

Cytology and biopsy are important for diagnosis (incisional biopsy prior to definitive surgery). The RLN should be palpated and assessed by FNA, or biopsy if enlarged.

Thoracic radiographs/CT should be taken as part of staging. CT/MRI scans of local tumour may be of use to plan definitive surgical resection. Removal with wide margins may be difficult due to location, especially if extensive local infiltration has occurred.

Radiation and chemotherapy may be used adjuvantly to surgery. This may improve survival times over surgery alone.

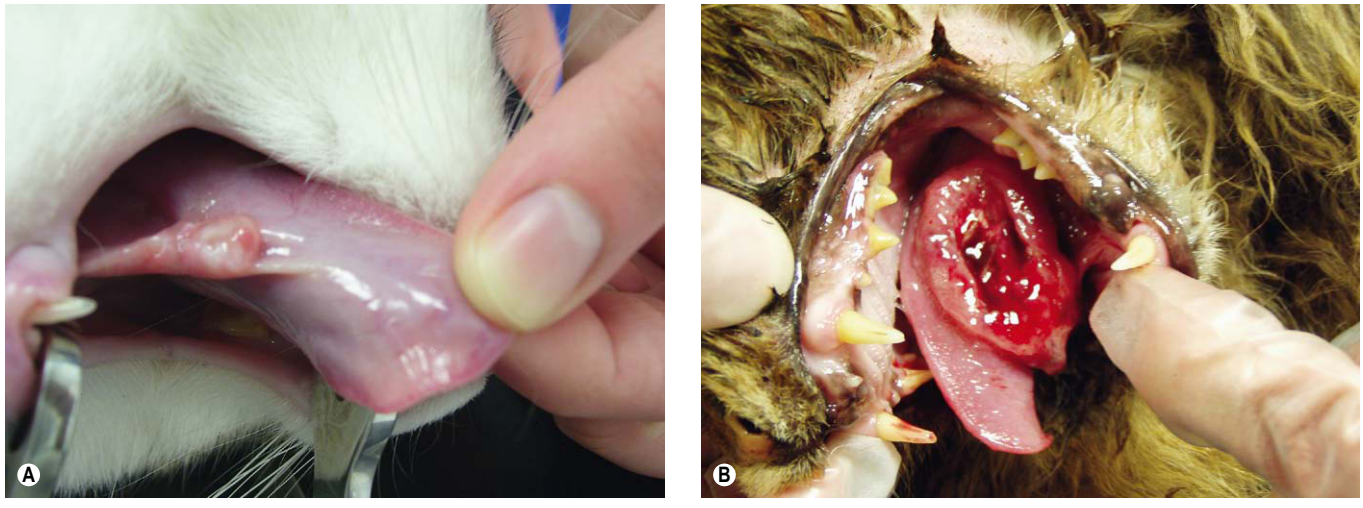


Figure 13.14 Sublingual squamous cell carcinoma in cats: (**A**) small and amenable to surgery; (**B**) large.

Early recognition is important because small tumours may be amenable to wide excision and an improved prognosis.

Histopathological features were not found to be prognostic in one study (Hammer et al 2001), although clinical stage was predictive.

Nasal tumours

Nasal planum tumours

SCC accounts for about 15% of skin tumours in cats (Miller et al 1991) and commonly affects the non-pigmented skin of the nasal planum, eyelid, periauricular skin and ear pinnae. Multiple lesions are found in about 30% of cats. SCC is correlated to repeated exposure to solar radiation and lack of protective pigment (actinic SCC). Siamese cats are uncommonly affected because of natural pigmentation in these areas. Older cats are generally affected, as solar radiation is a cumulative toxin. SCC progresses through a number of stages – very early crusting and erythema to preinvasive carcinoma (or carcinoma in situ) to progressively larger and deeper, more invasive, erosive, ulcerated and disfiguring lesions (**Figure 13.15**).

Differential diagnosis

Other tumours reported in this site are LSA, FSA, haemangioma, MM, MCT, HSA, fibroma, eosinophilic granuloma and histiocytoma.

History and clinical signs

Invasive SCC is usually preceded by a protracted course of disease (months to years).

Diagnostic work-up

Erosive or proliferative lesions should have a deep wedge biopsy to determine the degree of invasion and confirm diagnosis.

Cytology and superficial biopsies are not useful. Metastasis either to RLN or lung is rare, but as these are typically older patients, thoracic radiographs are advised before starting treatment.

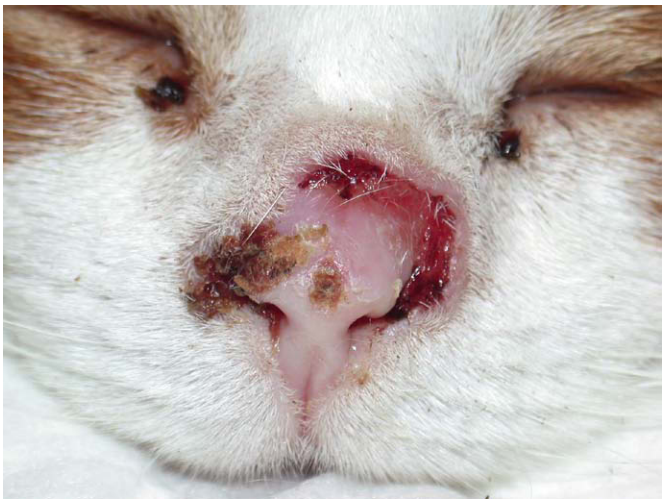


Figure 13.15 Squamous cell carcinoma of the nasal planum. (Courtesy R Straw.)

Treatment

Preneoplastic disease may be halted or limited by avoiding further exposure to sun (e.g. confinement to indoors). Synthetic derivatives of vitamin A may be helpful in reversing or limiting the growth of preneoplastic lesions (Evans et al 1985, Marks et al 1992). Repeated tattooing to add pigment protection is not very practical, and ineffective for ulcerated lesions. Topical sunscreens are readily licked off.

SCC can be divided into two categories:

1. *Superficial*: Minimally invasive disease (carcinoma in situ) can be managed effectively by surgery (for early lesions, removal of lesion with margins of 1–2 mm is generally sufficient), cryosurgery, lasers (Lana et al 1997, Shelley et al 1992), photodynamic therapy (PDT) (Peaston et al 1993, Stell et al 2001), intralesional carboplatin chemotherapy (Théon et al 1996), intralesional carboplatin and radiotherapy, external beam radiotherapy or brachytherapy (Fidel et al 2001, Lana et al 1997). Although the nasal planum can be preserved with non-surgical therapies, one downfall is a lack of documented 'clean' surgical margins (and the known removal of all local tumour).
2. *Deeply infiltrative disease*: Generally resistant to non-surgical treatments. External beam radiotherapy is recommended for larger lesions not amenable for surgery.

Surgery

Complete excision of invasive cancer of the nasal planum (nasal planectomy) can be performed in the cat (**Figure 13.16**) with an acceptable cosmetic result. Margins of 0.5 cm for superficial lesions, and 1 cm for deeper lesions (if possible), should be taken.

The skin incision is first marked out with a sterile pen and ruler, then a 360-degree skin incision that transects the underlying turbinates is made, and a 3-0 nylon purse-string suture is placed to create a new nasal orifice with a 1 cm diameter open circle (not too tight as it may heal across the airways). The scab formed is removed at sutures out. A possible delayed postoperative problem is stricture of the combined nasal orifice; this can usually be managed with resecting the strictured tissue. Functional and cosmetic results are fair to good.

Surgery is the treatment of choice for invasive lesions that have not extended extensively to lip or surrounding skin. Lana et al (1997) reported 61 cats with SCC of the nasal planum and pinnae, with 80% undergoing nasal planectomy free of disease at 1 year and an MST of 22 months. The attainment of clean margins correlated to prolonged survival.

Radiotherapy

If surgical margins are incomplete, adjuvant radiotherapy has been successful. Strontium brachytherapy is an option for microscopic disease after surgical excision. In one study (Hammond et al 2007) the median progression-free interval was 1710 days and overall survival time 3076 days, with an overall recurrence rate of 20%. Goodfellow et al (2006) reported good results for 15 cats treated with strontium plesiotherapy alone; 85% achieved a complete response, and these cats had no recurrence of disease during a follow-up period of 134–2043 days (median 652 days).

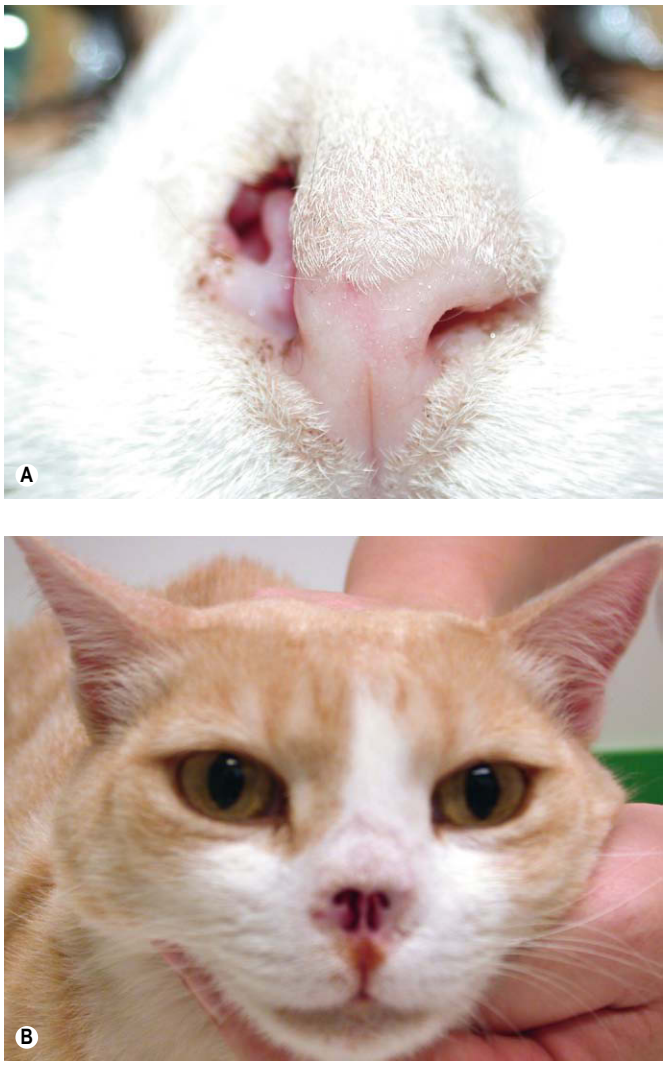


Figure 13.16 (**A**) Partial planectomy in a cat with squamous cell carcinoma. (**B**) Complete nasal planectomy. (Courtesy R Straw.)

Proton irradiation using an accelerated protocol in 15 cats gave a complete response in 60%, a partial response in 33% and no response in 6.6%. The 1-year tumour control rate was 64% (Fidel et al 2001).

In one report, external beam radiotherapy was evaluated in 90 cats; the median disease-free interval was 16.5 months (Théon et al 1995). However, this modality is recommended for more extensive lesions not suitable for PDT or strontium brachytherapy.

Photodynamic therapy (PDT)

A number of different studies have evaluated the efficacy of PDT in cats with superficial SCC. Results vary depending on tumour stage, photosensitizer used and route of administering the agent (see Chapter 8).

Peaston et al (1993) reported on 18 cats with SCC of the ear or nasal planum: one treatment was successful for 10 tumours, two or more tumours had complete responses after one or two additional treatments, and five tumours had partial responses. Treatments were more effective in T2 or earlier stage disease. Another paper reported an 85% complete response rate with a single PDT treatment; 64% of these later recurred at a median of 21 weeks (Stell et al 2001).

A different paper reported 15 cats treated with PDT. Complete response rates as well as local control durations were significantly ($P<0.05$) related to stage. Complete response was achieved in 100% of T1a tumours, 56% of T1b tumours and 18% of T2b tumours. One-year local control rates were 100% for T1a tumours and 53% for T1b tumours; overall 1-year local control rate for all treated tumours was 62% (Magne et al 1997).

Prognosis

The prognosis is good for early, non-invasive SCC. Later development of new sites of neoplasia on other areas of the planum or at other sites is common, because the underlying causes are not reversed. About 30% of cats developed new lesions at other locations in one study (Hammond et al 2007). Later stage disease can be cured with aggressive surgery or a combination of surgery and radiotherapy (Lana et al 1997).

Tumours of the nasal cavity

Nasal cavity tumours are less common in the cat than the dog, with LSA the most common (Henderson et al 2004, Mukaratirwa et al 2001). Other tumours include carcinomas and sarcomas. They tend to occur in older cats, with a mean age of 10.9 years, compared to nasopharyngeal polyps, seen in younger cats (mean age 13.6 months).

The first sign of neoplasia is typically a unilateral nasal discharge or epistaxis. A unilateral ocular discharge or epiphora was also significantly associated with neoplasia in 43 cats with sinonasal disease (Tromblee et al 2006). Other clinical signs may include sneezing, facial swelling, enlarged submandibular lymph nodes, weight loss and lethargy. Regional lymphadenopathy occurred in 21 of 123 cases of feline sinonasal cancer, but none of these lymph nodes were cytologically positive for metastasis (Mukaratirwa et al 2001). Differential diagnoses include Cryptococcus, nasopharyngeal polyp, nasal foreign body, Rathke's cleft cysts, salivary retention and nasopharyngeal stenosis (sequel to viral disease).

Diagnostic work-up for the cat is similar to the dog and a biopsy is required for confirmation of a nasal tumour.

The treatment of choice for cats with a nasal tumour is radiotherapy.

Prognosis

Nasal LSA is typically an isolated form of lymphoma. Survival times for patients with isolated nasal LSA is good to excellent. In one study of 19 cats with nasal lymphoma treated with radiotherapy and chemotherapy, the median progression-free interval for all cats was 31 months, and the MST was 31.4 months. The only variable found to have a significant negative impact on survival was destruction of the cribriform plate before therapy (Sfiligoi et al 2007). In another study, cats with nasal LSA treated with combination chemotherapy alone had an MST of 98 days (Henderson et al 2004). Most patients respond well to radiotherapy as sole treatment (**Figure 13.17**).

The prognosis for cats with non-lymphoid tumours is not as good, but survival times for cats with nasal carcinomas are

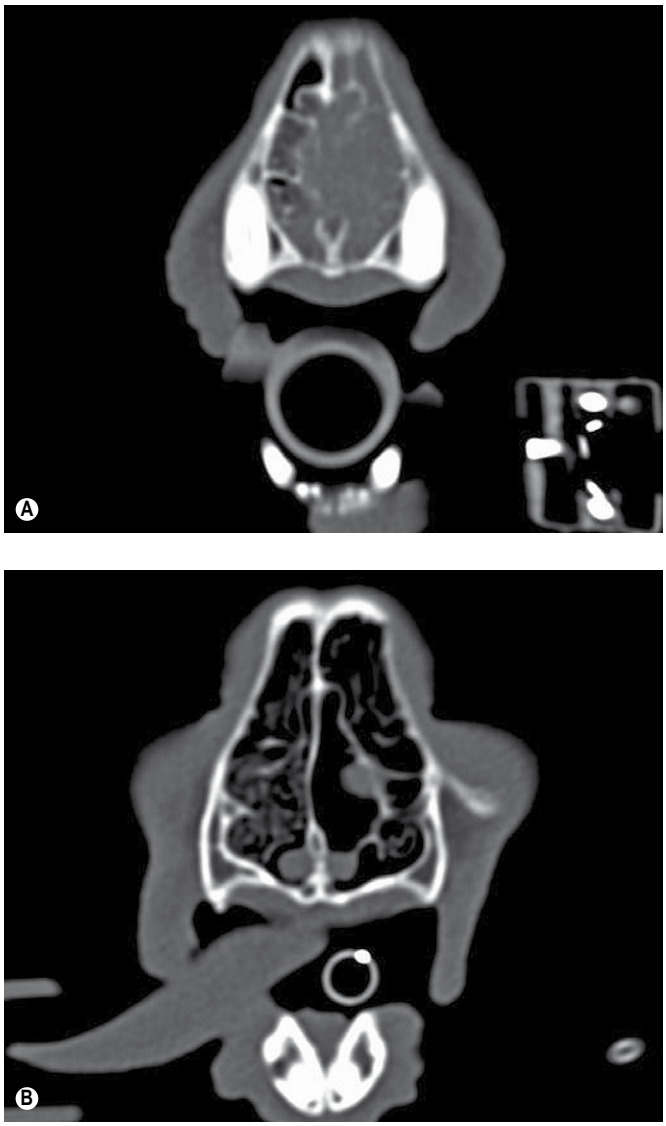


Figure 13.17 Nasal lymphoma in a cat. CT (**A**) before and (**B**) after 3 × 8 Gy radiotherapy using a 6 MV Linac.

comparable to those seen in dogs. Cats with nasal sarcomas do not respond well to radiation. A number of studies using different radiotherapy protocols have reported on small numbers of cats. Six cats with malignant nasal tumours treated with radiotherapy had an MST of 19 months (Straw et al 1986). Eight cats with non-lymphoid tumours treated with radiotherapy had an MST of 382 days (Mellanby et al 2002). Another study of 16 cats with non-lymphoid tumours had a 1-year survival of 44% and 2-year of 17% (Théon et al 1994b).

Ear tumours

Benign tumours are seen in slightly younger cats, mean age 7 years, compared to malignant tumours, mean age 11 years. The most common malignant tumour is ceruminous gland carcinoma (CGC). Malignant tumours show a 5–15% metastatic rate to RLN and lung at initial diagnosis. Neurological signs are present in up to 25% of patients with malignant tumours, especially SCC due to local invasion (London et al 1996). Malignant tumours are seen more frequently than benign. Benign tumours are usually raised and pedunculated with rare ulceration. Diagnostic work-up for ear tumours in cats is same as for dogs.

Prognostic factors

Poor prognostic factors include the presence of neurological signs, histopathology of SCC or undifferentiated carcinoma, and lymphatic or vascular invasion. Conservative surgery is also a negative prognostic indicator. The MST for cats with neurological signs was 1.5 months compared to 15.5 months without. The MST for cats with SCC was 4 months, undifferentiated carcinoma 6 months, and carcinoma 50 months. MST for patients with evidence of vascular/lymphatic invasion was 4 months, compared to 22 months without. Patients with carcinoma treated with lateral wall resection had a 10-month disease-free interval, 66% recurrence rate and 33% 12-month survival rate. By comparison, adenocarcinomas treated with TECA and bulla osteotomy had a 42-month disease-free interval, 25% recurrence rate and 75% 12-month survival rate (London et al 1996). The MST for cats with ceruminous gland carcinomas treated with TECA was about 50 months, and was no different from that achieved for inflammatory polyps (Bacon et al 2003).

Radiotherapy (48 Gy) has been reported to give a progression-free interval of 40 months, and 56% 12-month survival rate (Théon et al 1994a).

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Tumours of the larynx and trachea, mediastinum, chest wall and cardiopulmonary system

TUMOURS OF THE LARYNX AND TRACHEA

Laryngeal tumours

Cancers of the laryngeal region are rare in both dogs and cats. No breed predilection has been seen in either species. Benign laryngeal oncocytomas (rhabdomyomas) occur infrequently in young dogs (Meuten et al 1985, Pass et al 1980). Other types of benign laryngeal tumours include lipomas, leiomyomas, chondromas and osteochondromas.

Malignant tumours of the canine larynx include squamous cell carcinoma (SCC), adenocarcinoma, chondrosarcoma (CSA), osteosarcoma (OSA), rhabdomyosarcoma, mast cell tumours (MCT), plasma cell tumours and lymphoma (LSA) (Brodey et al 1969, Carlisle et al 1991, Crowe et al 1986, Flanders et al 1987, Hayes et al 2007, Saik et al 1986, Wheeldon et al 1982).

In cats, LSA and carcinomas are the most common tumours of the larynx (Jakubiak et al 2005, Vasseur 1981, Wheeldon & Amis 1985).

Tracheal tumours

Cancers of the tracheal region are also rare in both dogs and cats. In the former, the most common types are chondromas, osteomas, osteochondromas or carcinomas; young dogs can develop osteochondromas at less than 1 year of age that may be surgically excised with a good prognosis (Carb & Halliwell 1981, Dubielzig & Dickey 1978, Hough et al 1977).

Other benign tumours seen include leiomyomas and polyps (Black et al 1981, Bryan et al 1981). Uncommon canine tracheal malignancies include plasmacytomas, OSA, CSA, MCT, LSA, SCC and rhabdomyosarcoma (Chaffin et al 1998, Henderson et al 1991). In the cat the most commonly reported tracheal tumour is LSA; malignant epithelial and mesenchymal tumours have also been reported (Bell et al 2006, Evers et al 1994, Kim et al 1996, Lobetti & Williams 1992, Rossi et al 2007, Schneider et al 1979).

Neoplasia of thyroid gland, oesophagus, lung or aortic chemoreceptor may also invade the trachea.

Clinical signs

Dyspnoea, wheezing, coughing and stridor (may be inspiratory and expiratory) are the usual presenting signs (usually progressive). Occasionally, dysphagia and weight loss will be the major clinical signs. With laryngeal tumours changes in phonation may be noticed, and a mass may be palpable in the pharyngeal area. Clinical signs would be expected to worsen with excitement, stress, hot weather or exercise. Cats may cope better and for longer than dogs, as they are generally less active and excitable.

Diagnostic work-up

Radiographs will usually reveal a distinct mass or a narrowing of the lumen of the trachea around the laryngeal region. Laryngoscopy or tracheoscopy allows good visualization and sufficient access for biopsy in most cases. The anaesthetist should be prepared for an emergency temporary tracheostomy if normal laryngeal intubation is not possible. Biopsies should be taken (incisional) and impression smears made for cytology as well as tissue sent for histopathology. A single incisional biopsy was diagnostic in 22 of 27 cats (Jakubiak et al 2005).

Thoracic radiographs may be indicated for staging of disease, and may show signs secondary to upper respiratory tract obstruction (e.g. pulmonary oedema, pleural effusion, pectus excavatum). Regional lymph nodes (RLN) should be palpated for enlargement. Displacement of the local structures of the pharyngeal, neck or intrathoracic regions may be appreciated with further imaging, e.g. CT/MRI or radiographs.

Treatment options

Laryngeal tumours

Surgery

Benign laryngeal tumours (e.g. rhabdomyomas or oncocytomas) may be resected with preservation of normal laryngeal function, and have a good prognosis. In most malignant laryngeal cancers (**Figure 14.1**), total laryngectomy and permanent tracheostomy are required in the attempt to remove all local disease. One dog undergoing total laryngectomy and permanent tracheostomy for a laryngeal rhabdomyosarcoma had no evidence of disease 18 months after surgery (Block et al 1995). Pharyngeal dysphagia, local/distant tumour recurrence, care of a permanent tracheostomy wound, short- and long-term morbidity to the animal are factors for the client and clinician to consider carefully.

Radiation therapy and chemotherapy

If the tumour has a known responsiveness to chemotherapy or radiation therapy (e.g. if the tumour is of lymphoid origin), then this may be the best treatment option. However, it is important to obtain a definitive histopathological diagnosis prior to treatment. An incisional biopsy may also be therapeutic if it assists in the relief of upper respiratory tract obstruc-

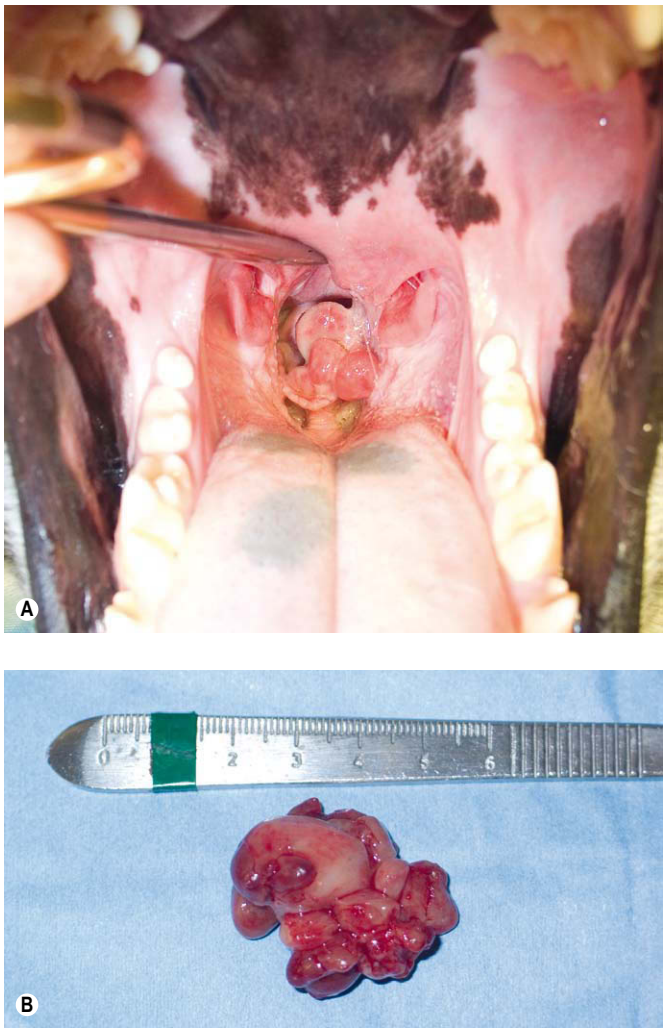

Figure 14.1 (**A**) Sarcoma of the epiglottis at presentation. (**B**) Sarcoma removed by partial laryngectomy.

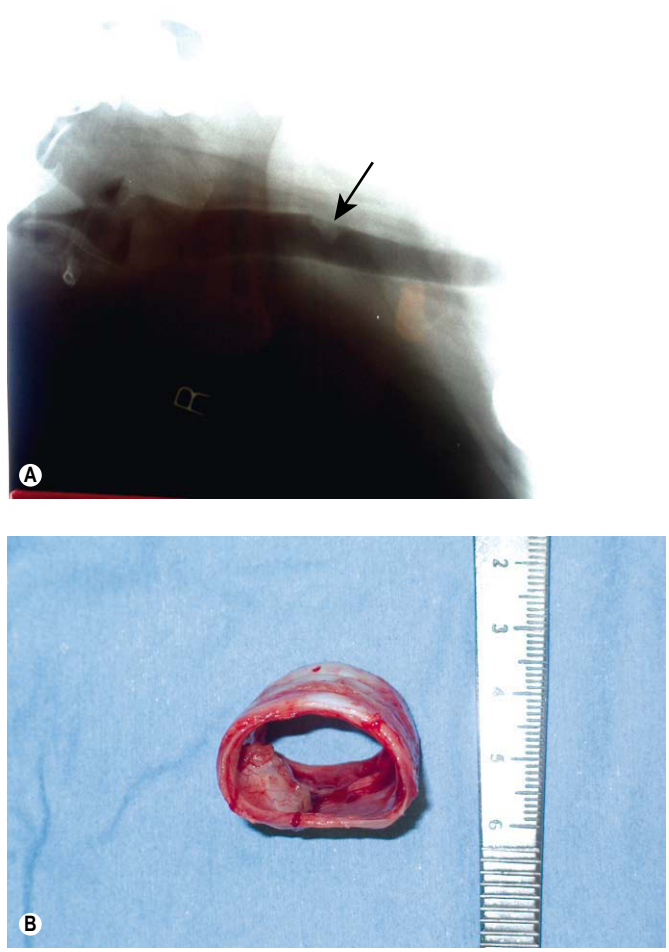

Figure 14.2 (**A**) Radiograph of a tracheal chondroma. (**B**) Excised chondroma.

tion. However, in cases of severe obstruction, an emergency debulking surgery may be required. This may allow initial palliation of clinical signs and provides tissue for diagnosis. It may be followed with adjuvant chemotherapy or radiotherapy, if considered beneficial.

For tumours not amenable to surgical excision without unacceptable morbidity as judged by the clinician and/or the client, surgical debulking and/or medical management may be indicated. Malignant laryngeal tumours generally have a poor prognosis, regardless of treatment.

Tracheal tumours

Surgery

Many tracheal tumours are benign and have a good prognosis with complete excision (**Figure 14.2**).

Surgery generally involves the resection of affected trachea and end-to-end anastomosis of tracheal rings. Tension is more of a problem in puppies than in adult dogs. Tension-free anastomosis is achievable if no more than 25–50% of the tracheal length (five or six tracheal rings) is removed in adult dogs and 20–25% in puppies (Nelson 2003). A simple continuous suture pattern is recommended (Demetriou et al 2006).

Tracheal wall replacement with latissimus dorsi (deficit <30% of ventral tracheal wall, <50% of dorsal tracheal wall and limited to five tracheal rings or less) has been successful (Fujita et al 1987). If fewer than five rings or >50% of the trachea is removed, reconstruction becomes more problematic. Rigid structures such as pedicled costal cartilage and rib, free cartilage, polypropylene mesh, collagen grafted mesh, mucous membrane grafted mesh, silicone rubber or non-porous silastic tubing can be used (Eckersberger et al 1987, Goldstein et al 1987, Kim et al 2004, Klopper 1969, Okumura et al 1994, Suh et al 2001, Yamato 1992).

Polytetrafluoroethylene grafts did not work in one study (Cull et al 1990) and jejunal autografts, with or without metal stenting, are sometimes successful but mostly unrewarding (Letang et al 1990, Ma et al 1990, Nakayama 1990, Szántó et al 2001).

Other treatment options

These include radiation, chemotherapy, endoscopic removal/debulking and photodynamic therapy. Chemotherapy is beneficial for tracheal LSA.

TUMOURS OF THE MEDIASTINUM

A number of tumours can be located within the mediastinum. The most common tumours located in this region are thymoma and lymphoma.

However, a number of other tumours and structures can also be seen, e.g.

- thymic carcinoma
- branchial cysts
- ectopic thyroid tissue
- chemodectoma
- metastatic disease
- other rare tumours, e.g. HSA, mesotheliomas
- local extension of rib or sternal tumours into the mediastinum.

Clinical signs

Clinical signs are usually respiratory in nature due to the space-occupying effect of a mass that can be of considerable size (**Figure 14.3A**). A pleural effusion may or may not be present. The most common presenting clinical signs are exercise intolerance or acute respiratory distress, and in some cases the patient can present with regurgitation due to compression of the oesophagus.

Precaval syndrome can be associated with mediastinal disease due to the obstruction of venous or lymphatic drainage from the head, neck and forelimbs. Paraneoplastic syndromes (PNS) are common with tumours in this region, especially LSA (e.g. hypercalcaemia) and thymomas (regurgitation) and often it is the paraneoplastic syndromes that alert the client to the fact there is a problem (**Figure 14.3B**).

Diagnostic work-up

For patients presenting with respiratory problems, precaval syndrome or regurgitation, thoracic radiographs are indicated (good quality right and left lateral and dorsoventral views). A cranial mediastinal mass may be accompanied by dorsal elevation of the trachea and oesophagus, caudal displacement of cardiac silhouette (depends on size) ± aspiration pneumonia, pulmonary metastasis (unusual) and pleural effusion (if invasive).

Patients presenting with other clinical signs may start off with a different work-up, e.g. for polyuria/polydipsia (PU/PD) routine blood work and urinalysis would be indicated, but any patient with documented hypercalcaemia requires thoracic radiographs. Haematology and biochemistry profiles are required in all patients with mediastinal masses as part of the diagnostic evaluation.

Obtaining a definitive diagnosis after confirmation of a mediastinal mass on radiographs is important because the definitive therapy for the major two differentials is completely different. Surgery is the treatment for thymoma, whereas chemotherapy is the major treatment for LSA.

How can we distinguish thymoma from lymphoma?

Signalment?

- *Cats*: Usually older cats have thymoma; younger cats have thymic lymphoma.
- *Dogs*: Thymoma is typically seen in older dogs; younger dogs are more likely to have lymphoma.

Clinical signs?

These can be similar for both tumours; however, PU/PD is more common with LSA, and regurgitation secondary to megaoesophagus is seen more frequently with thymomas.

Radiographic appearance?

As a mass in the cranial mediastinum, thymoma and lymphoma can be indistinguishable. The presence of other enlarged lymph nodes or abnormalities with other organ systems may indicate the origin of the mediastinal mass.

Presence of PNS?

Fifty per cent of dogs with mediastinal LSA are hypercalcaemic, whereas hypercalcaemia is less likely with thymoma. However, ultimately a tissue sample is required as paraneoplastic syndromes are not exclusive to one tumour type.

Additional diagnostic tests

Thoracic ultrasound

Ultrasound assists not only in delineating the size and echogenicity of a mass, but will also determine whether there is one or more masses in the mediastinum, i.e. the presence of metastatic disease within the mediastinal lymph nodes. It also facilitates diagnosis as fine needle aspirates (FNA) or tru-cut biopsies under ultrasound guidance can often be carried out.

Ultrasound can have difficulty in determining the full extent of a tumour regarding its invasiveness. Thymomas are often of mixed echogenicity and cavitated/cystic (compared to more homogeneous thymic LSA). Because they are cystic, thymomas may need a wedge biopsy for diagnosis.

CT/MRI scan

A CT or MRI scan can be very useful in determining the full extent and invasive nature of a tumour and assist the surgeon in presurgical planning. Wherever possible, a presurgical diagnosis is desired and this is usually attempted either by cytology or tru-cut biopsy.

Other diagnostic tests: thymomas

These include anti-acetylcholine receptor (ACh receptor) antibody titres (serology), Tensilon test to monitor for resolution of myasthenia gravis and immunohistochemistry (cytokeratin).

Thymoma

Thymomas are rare in both the dog and cat, with a median age of 9 years in the dog and 10 years in the cat. No breed

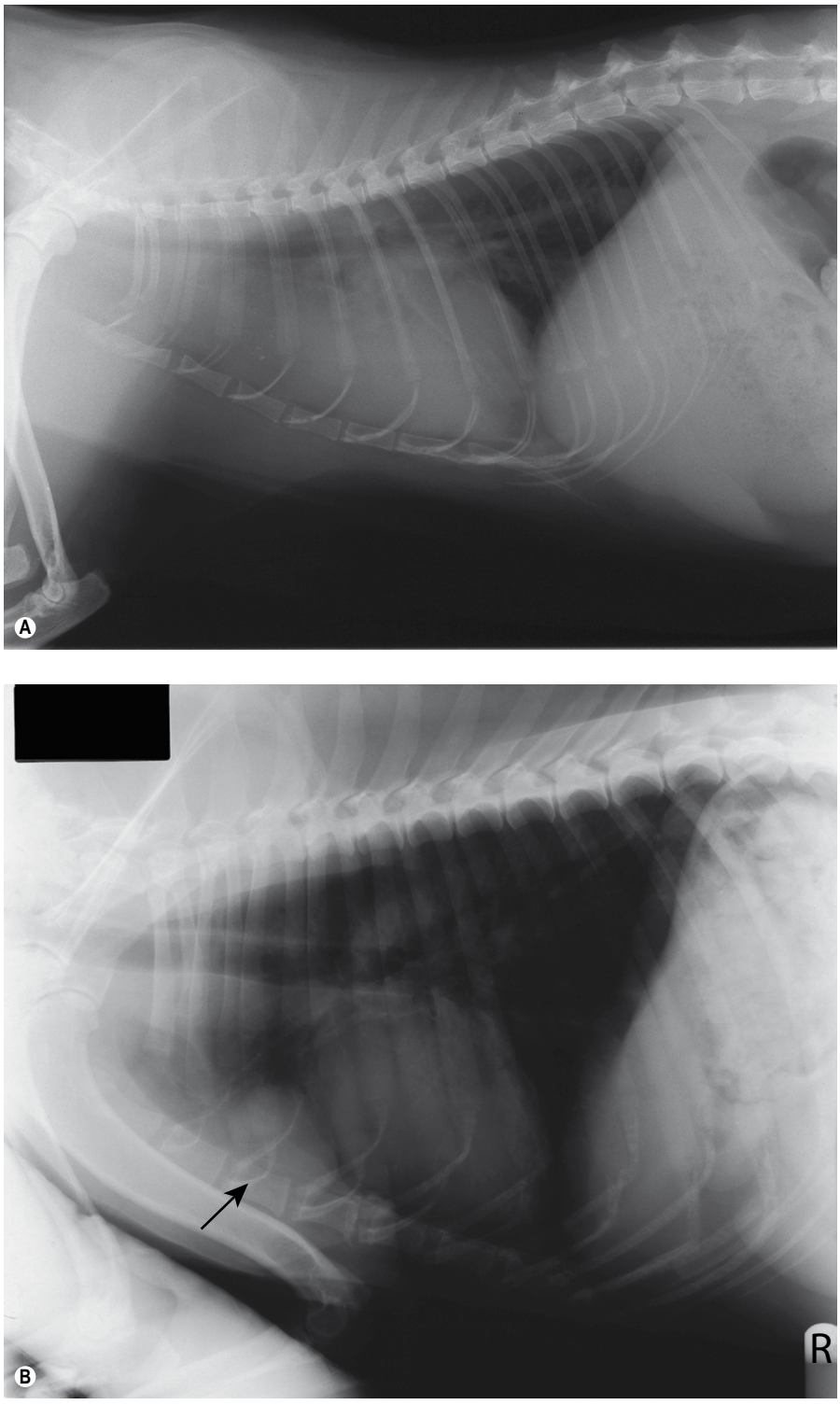

Figure 14.3 (**A**) Feline thymoma. (**B**) Canine thymoma.

or sex predilection has been noted in either species. Thymomas are usually slow-growing tumours and can therefore reach a considerable size before clinical signs are apparent.

Thymomas in dogs are located within the cranial mediastinum. They originate from the thymic epithelium and it is the epithelial component that is neoplastic. They are variably infiltrated with mature lymphocytes and variable numbers of mast cells may also be present. A number of histological types are recognized: lymphocyte-rich, differentiated epithelial and clear cell (Atwater et al 1994). Cytological confirmation of a thymoma rests on the presence of mature lymphocytes, mast cells and epithelial cells (Atwater et al 1994).

In many cases only lymphocytes are seen, making it difficult in some instances to rule out LSA. For this reason, cytology results are often not definitive and should be interpreted

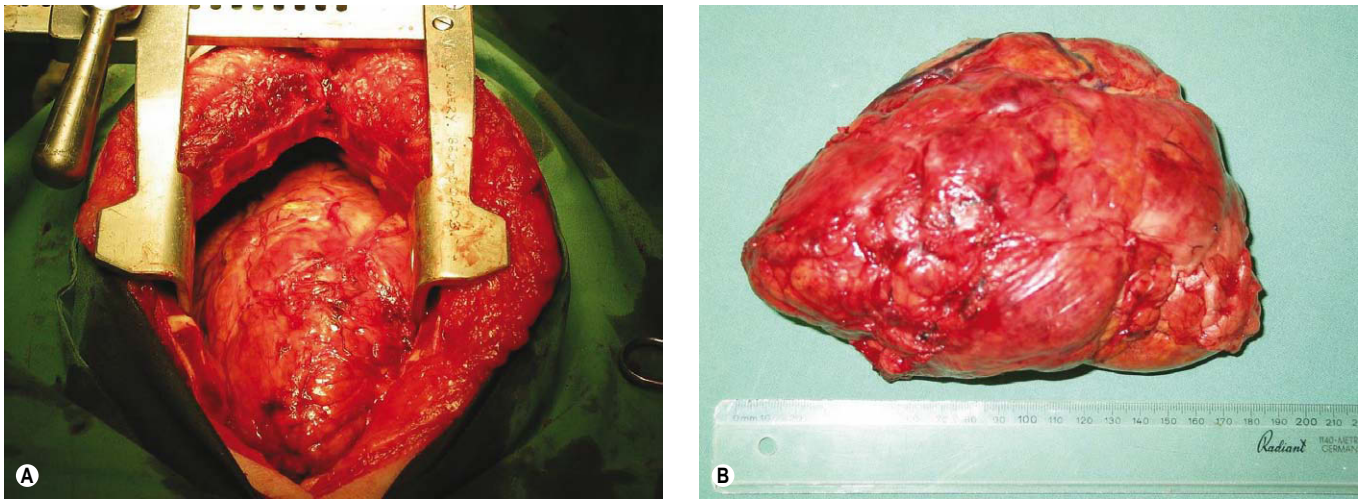

Figure 14.4 (**A**) Canine thymoma, intraoperatively. (**B**) Same patient, tumour removed. (Courtesy R Straw.)

with caution. Results of cytology after treatment with corticosteroids or chemotherapy can be even more misleading. A definitive diagnosis (with histopathology via needle core or wedge biopsy if necessary) should be sought prior to initiating any therapy. The definition of benign versus malignant resides primarily in resectability rather than histological features (Withrow 2007). Metastasis was reported in 3 of 14 cats (to RLN and lung) (Patnaik et al 2003).

Treatment of thymomas

- Surgery
- Radiation
- Chemotherapy

Surgery

Surgery is the treatment of choice for non-invasive thymomas, and can be curative (**Figure 14.4**).

For invasive thymomas, venous grafts can be performed for invasion of the cranial vena cava. For non-invasive thymomas, careful sharp/blunt dissection, with care of nerves and vessels, often allows removal. Both require thoracotomy via median sternotomy.

Resectability cannot be predicted or assessed until surgery. Size is not an indicator of resectability, and non-invasive thymomas can reach a very large size. Invasive thymomas will be adherent to surrounding tissues, including major vessels, nerves, trachea and oesophagus. Debulking an invasive tumour may alleviate symptoms and enhance the effectiveness of adjuvant treatments.

Radiation

There are few documented cases of radiation treatments in patients with incompletely resected thymomas. Thymomas are moderately radiation sensitive and with appropriate planning there is a role for radiation. Palliative radiotherapy would be an option in patients that were seen as poor surgical candidates due to other medical problems or PNS. For patients with large tumours, presurgical radiotherapy will reduce the size of the tumour very quickly, thus reducing respiratory distress associated with a large-space occupying lesion in the mediastinum. Typically, a single fraction of 800 cGy is sufficient and surgery can then be scheduled within 5–7 days of treatment. Radiotherapy is applicable for those tumours deemed unresectable by surgery.

Adjuvant radiation (combined with incomplete resection) has an increased survival time compared with incomplete resection alone. Complications include pneumonitis and pericarditis.

Chemotherapy

Although rarely considered in veterinary medicine, chemotherapy may be beneficial in patients that are not good surgical candidates and where radiation is not available.

Prednisolone may provide symptomatic relief by reducing the percentage of small lymphocytes in lymphocyte-rich thymomas. In humans, combination protocols utilizing doxorubicin/cisplatin/cyclophosphamide have been used. A definitive diagnosis of thymoma versus LSA versus other cancer should be sought before starting chemotherapy.

PNS and thymomas

A number of PNS have been reported in veterinary patients with thymomas. Myasthenia gravis has been reported in up to 40% of dogs (Atwater et al 1994) and is reported in cats (Gores et al 1994). The typical presentation is of muscle weakness and/or megaoesophagus, and 20–40% of patients have concurrent non-thymic neoplasms, autoimmune diseases, anaemia or polymyositis (Aronsohn et al 1984, Carpenter & Holzworth 1982).

If myasthenia gravis is present it requires treatment, because even if the tumour is treated successfully the symptoms may not resolve. Treatment comprises immunosuppression with prednisolone and the use of anticholinesterase drugs. Symptomatic treatment for megaoesophagus includes antacids ± antibiotics for aspiration pneumonia etc. Other syndromes usually resolve with adequate treatment of the thymoma.

Prognosis

Cats have an excellent prognosis when treated with surgery or radiation therapy. The median survival time with surgery is 21 months, and with radiation therapy is 24 months (Kaser-Hotz et al 2001, Smith et al 2001).

For dogs, the prognosis is excellent for non-invasive thymomas without megaoesophagus. When treated with surgery, these dogs have an 83% 1-year survival and often die of unrelated disease. The prognosis is guarded for invasive thymomas or if megaoesophagus is present (median survival time (MST) 4 days; with myasthenia gravis 67% died within 1 week) (Atwater et al 1994).

Dogs have a higher proportion of invasive thymomas compared to cats, which reflects on the overall improved survival of cats treated with surgery (MST approaching 2 years) (Gores et al 1994). If the tumour is not resectable, then prognosis is poor but survival times for these patients would undoubtedly be improved if they were considered for other treatment options, particularly palliative radiation. The MST for dogs treated with radiation therapy was 248 days (Smith et al 2001).

A recent study (Zitz et al 2008) reported even longer survival times in both cats and dogs treated with surgery alone (MST for cats 1825 days and for dogs 790 days).

Lymphoma of the mediastinum

This was the most common thymic tumour in one study in both cats and dogs (Day 1997). It is less circumscribed than thymoma, with local extension through the thoracic inlet around the heart base or into lung, pericardium, intercostal or cervical muscles.

Feline lymphoma

The classic feline patient with mediastinal lymphoma is a young cat (<2 years of age) that is feline leukaemia virus (FeLV) positive and has a poor prognosis even with doxorubicin-based chemotherapy (Peaston & Maddison 1999). The second peak is seen in older cats that are FeLV-negative and as an isolated form with a good prognosis (Teske et al 2002).

With the control of FeLV due to vaccination we now see cats of all ages with mediastinal lymphoma that are FeLV-negative. FeLV-negative cats younger than 4 years may have a particularly favourable prognosis when treated with multi-agent chemotherapy (Malik et al 2001). Young Siamese cats seem to be over-represented (Court et al 1997, Day 1997, Gabor et al 1998, Louwerens et al 2005, Peaston & Maddison 1999, Teske et al 2002).

Diagnosis is via clinical examination (non-compressible cranial thorax), radiographs (cranial mediastinal mass), cytology (thoracentesis or FNA of mass shows blasts rather than small mature lymphocytes), and biopsy if cytology is not definitive. Thoracic ultrasound often shows a homogeneous and hyperechoic mass compared to mixed echogenicity/cystic thymoma (Konde & Spaulding 1991).

Treatment

Chemotherapy

The majority of patients with mediastinal lymphoma are treated with combination chemotherapy (see Chapter 22 for protocols) and the overall prognosis depends on signalment, FeLV status and protocol.

Radiotherapy

Radiotherapy has a number of indications in the management of feline LSA. Due to the exquisite sensitivity of lymphoid tissue, radiotherapy can be used in the emergency situation when a patient is in significant respiratory distress. Relief within a few hours is possible. Radiotherapy can also be used for patients that are poorly responsive to chemotherapy, especially when they have undergone a relapse. Resistance to chemotherapy does not mean that there will be resistance to radiotherapy. Typical protocols include 5–8 Gy for up to three to four treatments (see Chapter 22).

Canine lymphoma

This is seen more commonly, although not exclusively in young dogs. No breed predisposition has been noted. The most common clinical presentations are respiratory signs, exercise intolerance, PU/PD or vomiting.

Mediastinal lymphoma accounts for ~5% of canine lymphoma (Theilen & Madewell 1987) and 20% of dogs with multicentric lymphoma have cranial mediastinal involvement (Starrak et al 1997). T-cell phenotype is more frequent; when seen in conjunction with hypercalcaemia the overall prognosis is guarded, with MST in the range of 6 months with combination chemotherapy (see Chapter 22).

Radiotherapy in canine mediastinal lymphoma has the same applications as in the feline counterpart and is used only in the emergency situation or when chemotherapy has failed as the first-line approach.

CHEST WALL TUMOURS

Malignant tumours of the chest wall are generally sarcomas. They usually arise from the ribs but can be sternal in origin. Benign tumours (osteomas and chondromas) and infection of bone or soft tissues are differential diagnoses for malignant tumours; however, the clinician should bear in mind that neoplasms can become necrotic or secondarily infected. Most commonly a mass on the chest wall is seen or palpated, and confirmed by radiographs. CT is useful to determine extent of local disease and resectability, and for the presence of pulmonary or lymph node metastasis.

A well-placed and well-executed incisional biopsy (see Chapter 5) is imperative prior to any attempt at surgical resection of a chest wall mass, for two reasons.

1. The prognosis depends greatly on the histological diagnosis, i.e. the client should know their pet's prognosis prior to embarking on a 'big' surgery (although en bloc resection of chest wall tumours involves minimal patient morbidity when performed by an experienced surgeon) (Baines et al 2002).
2. Smaller/debulking type surgeries only worsen the outcome and prognosis by compromising a potential curative resection of local tumour.

Any surgeon performing a chest wall resection should do so with the intent of removing all tumour tissue to obtain the best prognosis for the patient. A well-planned, expert, first surgical attempt will have the greatest chance of success (obtaining clean histological margins). Dirty margins increase the risk of recurrence or metastasis significantly (Pirkey-Ehrhart et al 1995).

The general rule for removal of a chest wall mass with clean margins is to include grossly and radiographically normal rib on either side of the tumour, and 3 cm margins dorsal and ventral to the tumour. Margins should be inked and the whole specimen sent for histopathology. Any adherent lung or other tissue must be removed with the mass, also with a 3 cm margin.

Chest wall reconstruction may be needed if more than three or four ribs are removed, and methods of achieving this include advancement of the diaphragm, latissimus dorsi flap and synthetic mesh or combinations (Matthieson et al 1992). Rib replacement with artificial ribs or grafting of contralateral autogenous ribs has been reported (Duan et al 2006, Tunçözgür et al 1999).

In general, the long-term prognosis for dogs with chest wall tumours is somewhat dependent on histological type. OSA has the poorest prognosis (Chapter 21) because of the high rate of metastasis, with MST of between 12 and 17 weeks for tumours treated with surgery alone (Baines et al 2002, Matthieson et al 1992). CSA and fibrosarcomas (FSA) had significantly longer MST due to the lower rates of metastasis, with MST for CSA ranging from 10 to 36 months (Baines et al 2002, Matthieson et al 1992, Pirkey-Ehrhart et al 1995). MST for FSA has been reported to range from 17 to 84 weeks with surgery alone (Baines et al 2002, Pirkey-Ehrhart et al 1995). Rib haemangiosarcoma (HSA), as expected, has a poor prognosis due to early metastatic spread (MST 90 days) (Pirkey-Ehrhart et al 1995).

LUNG TUMOURS

Primary lung tumours in dogs

These are uncommon tumours with a reported incidence of 4 cases per 100 000. Prevalence is increasing, however, which may be due either to increased longevity as primary lung tumours are typically seen in older dogs (median age is 10 years) or to increased exposure to secondary smoking. There appears to be a no particular breed or sex predilection.

The most common histological type seen is adenocarcinoma (bronchial, bronchoalveolar, alveolar), which comprises about 80% of primary lung tumours (Ogilvie et al 1989). Squamous cell carcinoma (SCC) is the second most common. Others include chondromas, sarcomas, adenomas, fibromas and plasmacytomas. Nodular lung disease (abscess, cyst, granuloma (e.g. fungal disease), parasite migration, heartworm disease) and canine pulmonary lymphomatoid granulomatosis (very rare) are differential diagnoses; lung lobe torsions may radiographically appear tumour-like.

Primary lung tumours in cats

Lung tumours in cats are also rare and again are typically seen in older cats; diagnosis also appears to be on the increase. Typically in cats the caudal lung fields appear to be most frequently affected (Hahn & McEntee 1997). Most primary lung tumours in cats are SCC, and 75% of feline primary lung tumours metastasize (Hahn & McEntee 1997) (**Figure 14.5**). In addition to local lymph nodes and other lung fields, metastasis may occur to multiple digits, and swollen toes and lameness may be the presenting clinical sign rather than respiratory signs. Amputation is not palliative and the prognosis for these patients is poor (Gottfried et al 2000, van der Linde-Sipman & van den Ingh 2000).

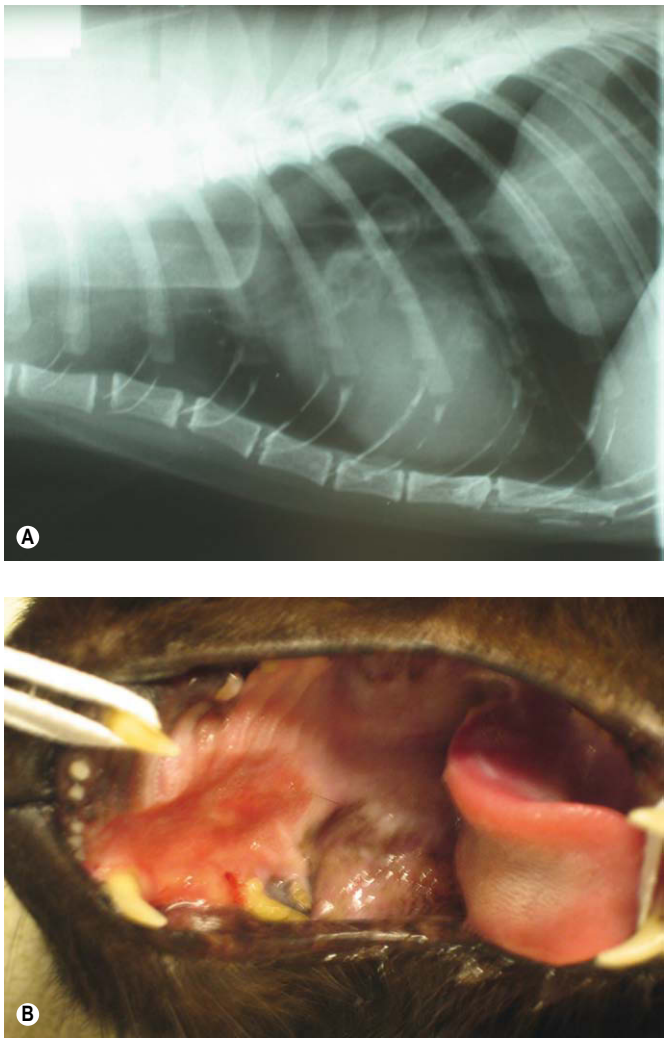

Figure 14.5 (**A, B**) Feline lung tumour with oral metastases. This cat also had multiple digital metastases.

Clinical signs

These can be the same in both species with a soft, dry cough that may respond initially to antibiotics but becomes more persistent. Patients may also present with weight loss, inappetence, exercise intolerance, lethargy, tachypnoea or dyspnoea. In some instances the presence of a pulmonary tumour may be an incidental finding when routine chest radiographs are taken for another purpose. Possible PNS include hypertrophic osteopathy (Brodey & Craig 1965, Madewell et al 1978, Sorjonen et al 1982), profound leucocytosis (Sharkey et al 1996), hypercalcaemia and pneumonia.

Diagnostic work-up

1. Thoracic radiographs (three views): Usually seen as a solitary, well-demarcated, spherical mass, often involving the caudal lung lobes (R > L). Uncommon diagnoses include pleural effusion, lymph node enlargement or multiple/miliary lesions (Bertazzolo et al 2002). Classify as solitary nodular, multiple nodular (usually one large

and smaller secondary) and disseminated/infiltrative. Nodules must be at least 7–9 mm diameter to be reliably seen on radiographs (Nemanic et al 2006). Also evaluate for hilar lymphadenopathy and pleural effusion. Inflated radiographs under general anaesthesia may be required to better evaluate lung fields.

2. CT scans are much more sensitive at picking up small metastases and will better define pulmonary lesions and lymph node enlargement (Nemanic et al 2006).
3. If pleural effusion is present, a sample should be submitted for analysis.
4. Thoracic ultrasound-guided aspirates of lung masses are of doubtful value, as inadvertent sampling of necrotic tumour centre will give a false result. Transthoracic FNA has been reported to be up to 80% accurate but with 12% mortality rate in cats and dogs. Thorascopy is a potentially valuable diagnostic tool.
5. Bronchoscopy/bronchoalveolar lavage (BAL): Transtracheal wash and BAL are usually only diagnostic in patients with lymphoma. Although these procedures are often performed in veterinary patients their value in cases of suspected primary lung tumours is limited as thoracotomy is essential for accurate diagnosis.
6. Complete blood count (CBC) and biochemistry may disclose a non-regenerative anaemia, leucocytosis or hypercalcaemia.

Treatment of primary lung tumours

Surgery (lung lobectomy) is the treatment of choice, provided there is no evidence of distant metastasis or extrapleural involvement. Treatment, excisional biopsy and prognosis are thereby attained with one procedure (**Figure 14.6**).

Partial lung lobectomy can be performed if the tumour is at the periphery of the lung lobe, otherwise total lung lobectomy with the widest margins possible is performed. An intercostal thoracotomy (usually fifth intercostal space) is preferred over median sternotomy, as it allows better exposure for lung, both lobectomy and lymph node biopsy (important for staging purposes and prognosis).

Experienced surgeons using specialized surgical stapling equipment reliably and efficiently remove lung lobes. These staples provide the surgeon with the assurance of a leak-free seal, of particular importance in handling delicate lung tissue.

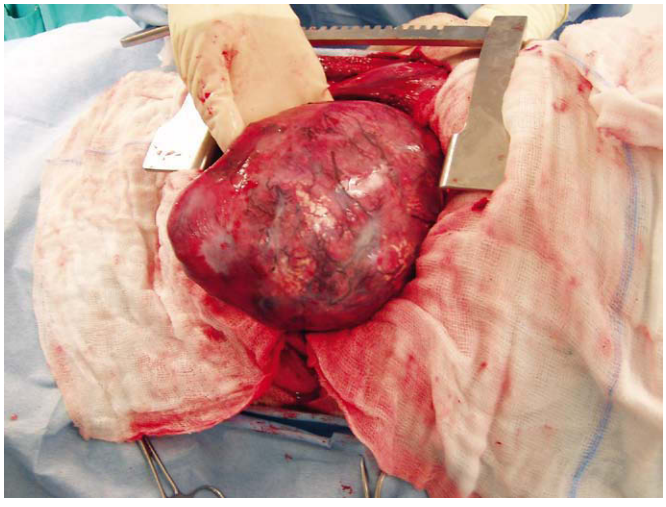

Figure 14.6 Canine lung tumour.

Prognosis

The overall MST is 12 months for dogs (McNiel et al 1997) and 115 days for cats (Hahn & McEntee 1998) (when treated with surgery alone).

Prognostic factors in dogs

1. Perihilar lymph node involvement is the most important prognostic factor. The MST is 1–2 months for positive lymph nodes, versus 12–15 months if lymph nodes are negative for metastatic disease (McNiel et al 1997, Ogilvie et al 1989). MST was 555 days for T1N0M0 primary lung tumours (papillary type) and 72 days for the remainder (Polton et al 2008).
2. Histological grade is important for primary pulmonary adenocarcinomas (80% of primary lung tumours in dogs). In one study (McNiel et al 1997), well-differentiated tumours showed an MST of 790 days and a median disease-free interval (MDFI) of 493 days; in moderately differentiated tumours the MST was 251 days and MDFI 191 days; and in poorly differentiated tumours the MST was 5 days and MDFI 0 days.
3. Site: Peripheral lobe tumours have an MST of 16 months compared to 8 months if the entire lobe is affected (Mehlhaff et al 1984).
4. Cell type: Dogs with primary pulmonary adenocarcinoma have an MST of 19 months compared to 8 months for primary pulmonary SCC (Mehlhaff et al 1984). MST for low-grade papillary carcinoma is 17 months compared to 1.5 months for all other cell types (McNiel et al 1997).
5. Size: Tumours <5 cm diameter have an MST of 20 months compared to 8 months for those >5 cm diameter (Mehlhaff et al 1984).
6. Coughing dogs have an MST of 8 months compared to 18 months for dogs without a cough (McNiel et al 1997).

Prognostic factors in cats

The degree of tumour differentiation is the only prognostic factor in cats, with the MST for well-differentiated tumours in cats of 23 months, compared to 2.5 months for cats with undifferentiated tumours (Hahn & McEntee 1998). Cats with perihilar lymph node metastasis have an MST of 73 days versus 412 days for those without lymph node involvement. The MST for cats with metastatic lesions in their digits is 58 days.

Metastatic pattern

Like most carcinomas, primary lung tumours will spread to the draining (hilar) lymph nodes and then to other lung lobes. In some cases a malignant effusion may result. In the cat an unusual site of metastases are the digits or musculoskeletal system.

Secondary (metastatic) lung tumours

These are much more common than primary lung tumours (**Figure 14.7**). The radiographic appearance of metastatic lung

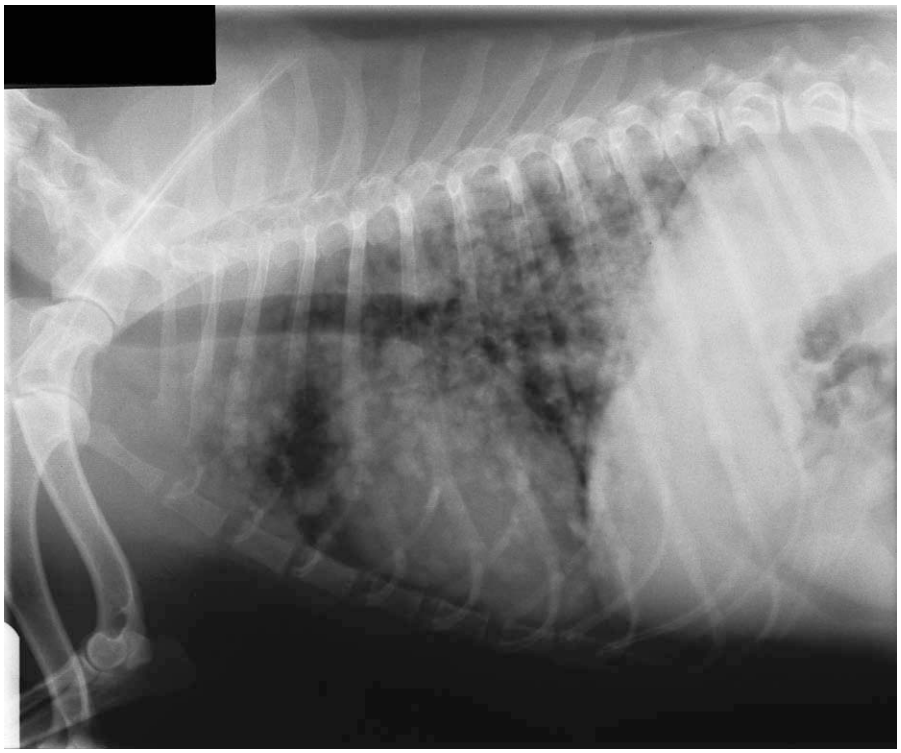

Figure 14.7 Pulmonary metastases.

cancer differs in dogs and cats. In cats, the most common radiographic presentation of metastatic disease is ill-defined pulmonary nodules, alveolar disease, pleural effusion or a combination of these (Forrest & Graybush 1998). Epithelial neoplasms are the most common metastatic tumours in cats. In dogs, pulmonary metastatic disease most commonly appears as multiple circumscribed, interstitial nodules, although a diffuse alveolar pattern is occasionally seen with LSA, metastatic mammary carcinoma, diffuse alveolar carcinoma and metastatic HSA secondary to haemorrhage.

In veterinary medicine the management of secondary neoplasia to the lungs is limited. Malignant effusions can be treated with intracavitary chemotherapy (cisplatin). Although these effusions are usually associated with mesotheliomas, carcinomas can be treated in the same fashion (Moore et al 1991).

Metastectomies can be carried out when a small number of stable metastases are present, most often applicable to slowly metastasizing sarcomas. The indications for pulmonary metastectomy are a metastasis-free interval of >300 days, prior exposure to effective chemotherapy, favourable histology, no other known metastatic sites, >40-day doubling time and fewer than three radiographically visible nodules. Dogs that developed pulmonary metastases 300 days or more after diagnosis of a primary appendicular OSA (treated with amputation or limb sparing and adjuvant chemotherapy ± local radiation therapy) had an MST of 176 days and a 28% 1-year survival after metastectomy (O'Brien et al 1993).

Adjuvant systemic chemotherapy is recommended in tumours with known biological behaviour that will metastasize to the lungs, e.g. OSA. Systemic chemotherapy is rarely given when pulmonary metastases from sarcomas or carcinomas are visible on radiographs because of the overall poor prognosis in these cases. However, this does not mean that veterinary patients may not have short-term benefit from systemic chemotherapy in the presence of gross metastatic disease.

Inhalational chemotherapy, using either taxol or doxorubicin every 2 weeks, for primary and metastatic lung tumours (Hershey et al 1999) showed responses to sarcomas but not carcinomas. Response rate was 25% (6/24) with five partial and one complete response, with no systemic toxicities.

MESOTHELIOMA

Rare in both the cat and the dog, mesothelioma is typically seen in older animals. Embryologically, mesothelial cells originate from the mesoderm and mesotheliomas are divided into three histological types:

- epithelial – the most common type
- mesenchymal
- mixed.

Clinical signs

Clinical signs are usually associated with fluid production. These tumours are malignant due to their ability to seed throughout a cavity, but they rarely metastasize.

Diagnostic work-up

- Fluid analysis: can be diagnostic, but often only a modified transudate is present.
- Radiographs: usually only visualize fluid.
- CT.
- Surgical exploratory.

Treatment

Surgery

Mesothelioma generally presents as a poorly circumscribed, diffuse disease that is not amenable to surgical resection. The role of surgery is usually only to obtain a definitive diagnosis via incisional biopsy.

Chemotherapy

In dogs intracavitary cisplatin is the drug of choice. Intracavitary instillation is usually done at a dose of 50 mg/m^2. Diuresis before and after treatment is recommended, and the treatment can be repeated every 3 weeks until symptoms resolve. Cisplatin only penetrates small masses (2–3 mm) and therefore is only appropriate in selected cases. It is well tolerated, with some long-term survivors (up to 1 year, one dog at 807 days) (Moore et al 1991).

Systemic chemotherapy ± intracavitary therapy for larger tumours may be beneficial.

TUMOURS OF THE CARDIOPULMONARY SYSTEM

HSA is the most common cardiac tumour in dogs, specifically the right atrium (right auricular appendage). Chemodectoma of the aortic body is the second most common. Other tumours seen include sarcomas (FSA, OSA, CSA), mesothelioma, myxoma and ectopic thyroid carcinoma.

Secondary LSA is the most common cardiac tumour in cats. Tumours metastatic to the heart include HSA, LSA, mammary gland carcinoma, salivary gland carcinoma and MCT.

Auricular HSA

This is most commonly seen in German Shepherds, Golden Retrievers and Labrador Retrievers.

Clinical signs

These include cardiac tamponade – signs of right heart failure leading to collapse/acute death, dysrhythmias, muffled heart sounds and ascites. Typically leading up to the more acute clinical signs, the client may have noticed increased exercise intolerance and dyspnoea.

Diagnostic work-up

1. Echocardiogram to exclude pericardial effusion: a tumour is not always visualized and the major differential to be excluded is idiopathic pericardial effusion.
2. Chest radiographs to exclude cardiomegaly: the heart is typically enlarged, and there may also be pleural and abdominal effusion.
3. ECG: typical findings include low amplitude QRS and electrical alternans.
4. Fluid analysis: if a tumour has not been unequivocally identified, fluid analysis may be beneficial.
5. Blood work: haematology may reveal low-grade anaemia, leucocytosis or no significant abnormalities.
6. Abdominal ultrasound is necessary to determine whether the auricular tumour is primary or secondary.

Treatment of primary auricular HSA

There is one case report on the resection of a right atrial mass with clean margins (only atrial appendage/atrial free wall involved) and reconstruction with a pericardial patch graft (Brisson & Holmberg 2001). However, the survival time was poor (4 months), and death was due to metastatic disease. Primary cardiac HSA of the right atrial appendage also has a poor prognosis with resection (4-month MST) (Aronsohn 1985). Dunning et al (1988) reported an MST of 16 days post-surgery for HSA involving the pericardium, but 15.3 months for mesothelioma.

Adjuvant chemotherapy has been tried in dogs with right atrial HSA treated with surgery (pericardiectomy and tumour resection) to try to prolong survival times (Weisse et al 2005). The MST was 175 days for 8 dogs that received adjuvant chemotherapy, compared to 42 days for 15 dogs that did not receive chemotherapy.

Palliative treatment options include pericardiocentesis/pericardiectomy and the medical management of dysrhythmias.

Chemodectoma/aortic body tumour/carotid body tumour

Risk increases with chronic hypoxia, so these tumours are more common in older brachycephalic breeds (Boxer, English Bulldog, Boston Terrier) (Dean & Strafuss 1975) and rare in cats. Of 22 canine cases, 9 had concurrent aortic and carotid body tumours (Dean & Strafuss 1975). Chemoreceptor cells (sensitive to oxygen and carbon dioxide tension in the blood and involved in regulation of the heart and respiratory rate) are present in clusters at the carotid bifurcation (carotid body) in the neck and aortic root (aortic body) at the heart base (80%). These tumours are highly vascular and slow growing with moderate local invasiveness and low metastatic rate. They have a propensity for local invasion of vascular and lymphatic structures. Metastasis has occasionally been reported (Carlisle et al 1978, Feher & Roullard 1977, Gliatto et al 1987, Kim et al 2005, Montgomery et al 1980). They can be associated with other endocrine tumours (Evans et al 1986).

The clinical signs vary depending on size and location of the tumour. The most common presentation is due to intrapericardial haemorrhage, causing decreased cardiac output, weak pulses, arrhythmias and abdominal effusion. Aortic body tumours can also cause right-sided congestive heart failure secondary to obstruction of the atria ± vena cava, with clinical signs as described for right atrial HSA. The diagnostic approach is the same as for HSA, and a biopsy is of benefit.

Treatment is surgical (pericardiectomy) with a few long-term survivors. Pericardiectomy provides a better prognosis (MST 730 days) than chemotherapy and diuretics (42 days), independent of the presence or absence of pericardial effusion (Ehrhart et al 2002). In 25 dogs with heart-based masses, those treated with pericardiectomy had a significantly longer survival (mean 661 ± 170 days) than those treated medically (mean 129 ± 51 days) (Vicari et al 2001).

Carotid body tumour is typically seen as a cranial cervical mass for which the main differential is a thyroid tumour. They are locally invasive and have the propensity to metastasize to

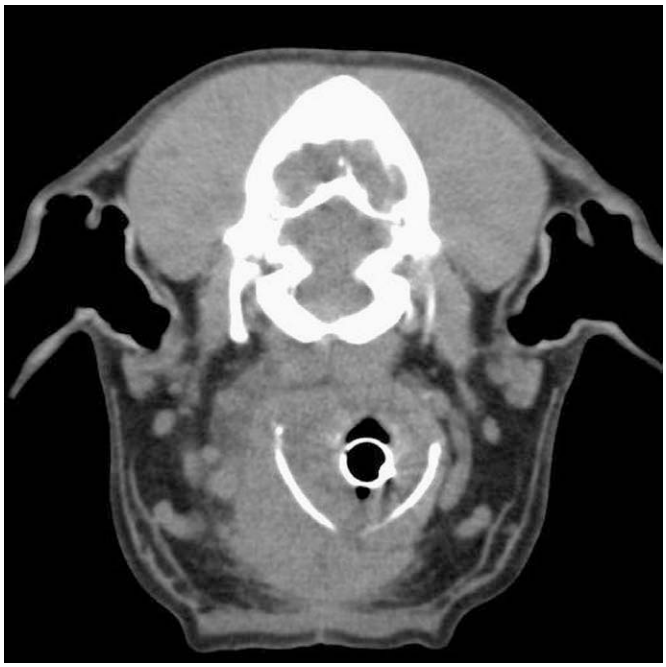

Figure 14.8 CT scan of carotid body tumour.

multiple sites. Treatment is surgery or radiation. Prognosis is 40% perioperative morbidity due to laryngeal paralysis and Horner's syndrome. The MST is 25.5 months with surgical resection (Obradovich et al 1992). For those with inoperable disease, palliative radiotherapy will shrink and stabilize the tumour, providing improved quality of life (**Figure 14.8**).

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Tumours of the gastrointestinal tract and associated structures

Oesophageal tumours (canine and feline)

Oesophageal cancer in cats and dogs is very rare. The most common types are squamous cell carcinoma and other carcinomas, leiomyosarcoma, fibrosarcoma and osteosarcoma (Gualtieri et al 1999a, Jacobs & Rosen 2000, McCaw et al 1980, Ranen et al 2004a, Shinozuka et al 2001, Takiguchi et al 1997).

There are also reports of benign tumours, e.g. leiomyoma and plasmacytoma, especially in the terminal oesophagus and cardia (Culbertson et al 1983, Hamilton & Carpenter 1994, Rolfe et al 1994). Sarcomas secondary to *Spirocerca lupi* have been reported (Ranen et al 2004b). Most malignant oesophageal tumours are locally invasive and metastasize to draining lymph nodes and/or haematogenously. Secondary invasion of the oesophagus by other neoplasia can also occur, e.g. thyroid or heart base tumours.

Clinical signs

These include oesophageal disease (regurgitation, dysphagia, pain on swallowing, aspiration pneumonia).

Diagnostic work-up

Thoracic radiographs may show soft tissue opacity in the thorax, an abnormal gas shadow in the oesophagus, or signs of aspiration pneumonia. A positive contrast study may show narrowing of the oesophageal lumen; however, the clinician should take extreme care that no contrast agent is aspirated into the lungs.

Due to the risk of aspirating contrast agent, it may be preferable to diagnose the presence of an oesophageal mass with endoscopy, which also provides an opportunity for endoscopic biopsies to be taken. If the tumour is a leiomyoma or leiomyosarcoma (arising from the smooth muscle of the oesophageal wall), and it has not perforated/ulcerated through the submucosa into the oesophageal lumen, retrieval of a diagnostic biopsy specimen using endoscopy may be difficult. However, the visualization of a non-ulcerated, submucosal, well-circumscribed spherical mass is suspicious of a leiomyoma or leiomyosarcoma. An ulcerated mass may be more amenable to diagnosis via endoscopic biopsy.

If endoscopic biopsies are unhelpful, the surgeon may then choose to attain a larger sample of tumour for definitive histopathological diagnosis via a thoracotomy. An attempt at curative resection/excisional biopsy would then be appropriate if the tumour appeared excisable.

Treatment

The treatment of malignant oesophageal cancer is difficult at best. Contributing factors are poor exposure, lengthy resections, tension, difficulty in reconstruction of oesophageal deficits, and metastatic disease. Radiation is of limited value. The prognosis is generally very poor for malignant oesophageal cancer. The prognosis for benign smooth muscle tumours is excellent with curative surgical resection. In the rare diagnosis of oesophageal plasmacytoma or lymphoma, a good prognosis may also be expected. Solitary plasmacytomas may be completely excised; however, if this is not possible, chemotherapy is recommended, usually a combination of cyclophosphamide and prednisolone for a number of cycles until no tumour is visible on endoscopy.

If more than 3–5 cm (more than 20%) of oesophagus is removed, there is an increased chance of dehiscence due to tension (Hedlund 1997). Partial circumferential tears are less likely to cause stricture formation than complete circumferential tears. Repair can be augmented with muscle and omental flaps. Few papers have been written on oesophageal replacement for large defects. Successful replacement of cervical oesophageal defects with microvascular anastomosis of free autogenous jejunal grafts has been reported in 20 dogs (Bouayad et al 1993), and in one other dog (Gregory et al 1988). However, only 4 of 20 dogs survived when the jejunal graft replaced the thoracic oesophagus, mostly due to leakage into the thoracic cavity (Bouayad et al 1993).

Free autogenous colon grafts used to replace thoracic oesophagus failed in five of five dogs, but were successful in three of three dogs when used to replace part of the cervical oesophagus (Kuzma et al 1989). A technique of substituting thoracic oesophagus with a vascularized, tubed transversus abdominus muscle graft had a high risk of complication and mortality, and was proven unsuitable (Straw et al 1987). In a recent paper, four of seven dogs survived reconstruction of partial circumferential defects of the thoracic oesophagus with pedicled diaphragm flaps (Paulo et al 2007).

Gastric tumours

Canine gastric tumours

Tumours of the stomach are uncommon, and account for <1% of all tumours encountered in the dog. Average age is 8 years and males are more commonly affected with gastric adenocarcinoma and lymphoma (Couto et al 1989, Priester & McKay 1980, Sautter & Hanlon 1975).

Adenocarcinoma accounts for 70–80% (Swann & Holt 2002), and is more common in Belgian Shepherds, Collies and Staffordshire Bull Terriers (Gualtieri et al 1999b, Sullivan et al 1987). French Bulldogs are predisposed to gastric adeno-

mas, which can cause gastric outflow obstruction (Neiger 2003). Adenocarcinomas are often scirrhous (firm and white serosally) and appear leathery.

Other tumours are leiomyosarcoma (second most common tumour) (Kapatkin et al 1992, Swann & Holt 2002), leiomyoma (Kerpsack & Birchard 1994) and lymphoma (Couto et al 1989). Rare stomach tumours include extramedullary plasmacytoma (Brunnert et al 1992), mast cell tumour (Ozaki et al 2002), fibrosarcoma, adenomatous polyp, squamous cell carcinoma, fibroma, and carcinoid tumours of the enterochromaffin cells (Neiger 2003).

In one study (Swann & Holt 2002), 74% of dogs with gastric adenocarcinomas had metastasis. Gastric adenocarcinomas occur most commonly at the lesser curvature and antrum (Withrow 2007). Leiomyomas often occur at the cardia, and grow into the lumen as a smooth, well-circumscribed mass (Kerpsack & Birchard 1994). Gastric lymphoma as an isolated tumour is rare in the dog.

Feline gastric tumours

Feline lymphoma is the most common gastric tumour in the cat. Affected cats tend to be younger and are often feline leukaemia virus (FeLV)-negative. Gastric lymphoma can be localized or diffusely infiltrative. Other tumours are rare in cats.

Clinical signs

These include progressive intermittent vomiting (often haematemesis), weight loss and inappetence/anorexia.

Diagnostic work-up

- Radiography
- Ultrasonography
- Endoscopy
- Routine blood tests

Radiography

Positive contrast radiographic studies may show a filling defect or an outflow obstruction.

Ultrasound

Ultrasound of the stomach wall has been shown to be a useful, sensitive tool to detect tumour (Lamb & Grierson 1999, Rivers et al 1997) and has the advantage of showing disruption to the layers of the gastric wall (infiltrative vs. non-infiltrative tumours) and is usually the diagnostic tool of choice. Ultrasound may also be useful for staging the disease (e.g. evidence of lymphadenomegaly, or metastasis to other abdominal organs). However, these images do not provide definitive histopathological confirmation of metastatic disease, and should be interpreted with caution. For example, liver and splenic nodules may be benign nodular hyperplasia and enlarged lymph nodes may be a reactive change. Ultrasound-guided fine needle aspirates of thickened stomach wall may be useful; however, endoscopic biopsies are generally preferable.

Endoscopy

Endoscopy (gastroscopy) is a very useful tool to diagnose the presence of tumour and for collection of biopsy samples. However, endoscopic biopsy samples are small and are not always diagnostic because of associated necrosis, inflammation and fibrosis, and surgical biopsy may be the only method of obtaining a reliable diagnosis.

Routine blood tests

Non-regenerative, normocytic, hypochromic anaemia may result from chronic blood loss. Vomiting can cause hypochloraemia, hypokalaemia and a metabolic alkalosis. Paraneoplastic hypoglycaemia may be seen with leiomyomas and leiomyosarcomas (Bagley et al 1996, Beaudry et al 1995, Bellah & Ginn 1996, Boari et al 1995).

Staging

Staging is undertaken using abdominal ultrasound (see above comments) and thoracic radiographs.

Treatment and prognosis

The treatment of choice for most gastric tumours is surgery. Treatment is complicated by stage of disease at presentation and difficult operative area, often with a debilitated patient. A wide partial gastrectomy should be performed if possible. A 'Bilroth I' (partial gastrectomy with preservation of the pancreas, pancreatic duct and bile duct) is much better tolerated than a 'Bilroth II' (partial gastrectomy, pancreatectomy and cholecystoduodenostomy). Pancreatic exocrine insufficiency, dumping syndrome and bacterial intestinal overgrowth are some of the complications associated with Bilroth II, causing significant patient morbidity (Ahmadu-Suka et al 1988). Smaller, more frequent feeds may be required with resection of >25% of the stomach wall.

Gastric lymphoma

Diffuse gastrointestinal lymphoma does not respond well to standard chemotherapy (Couto et al 1989), so if excision is possible, it is advised. In the authors' opinion, if gastric lymphoma appears as a mass lesion rather than generalized thickening, it should be treated with surgical excision if possible, and if not, with debulking and adjuvant chemotherapy. A liver biopsy should be taken for staging purposes, and regional (mesenteric) lymph nodes should also be biopsied/removed if enlarged.

For dogs with isolated gastric lymphomas treated with complete excision with adjuvant chemotherapy, the prognosis may be better than had been previously thought. However, for those patients where the tumour cannot be excised or is not confined to the stomach, the prognosis is poor, even with combination chemotherapy (3–6 months) (Couto et al 1989).

Gastric adenocarcinomas

These tumours should be removed with 1–2 cm margins of grossly normal tissue if possible. Even with successful resection with clean margins, the prognosis for adenocarcinomas is poor, with most animals dead within 6 months (Elliott et al 1984, Olivieri et al 1984, Swann & Holt 2002). Chemotherapy and radiation therapy are not of any known benefit in animals with gastric adenocarcinomas. Anecdotally, response to gemcitabine has been reported. In theory, total gastrectomies can be performed (Sellon et al 1996); however, this is rarely seen as a viable option in veterinary medicine.

Gastric leiomyosarcomas

The median survival time for dogs with gastric leiomyosarcoma is better at approximately 1 year (Kapatkin et al 1992).

Gastric leiomyomas

Often discovered as an incidental finding during necropsy, surgery or endoscopy in the old dog, gastric leiomyomas can

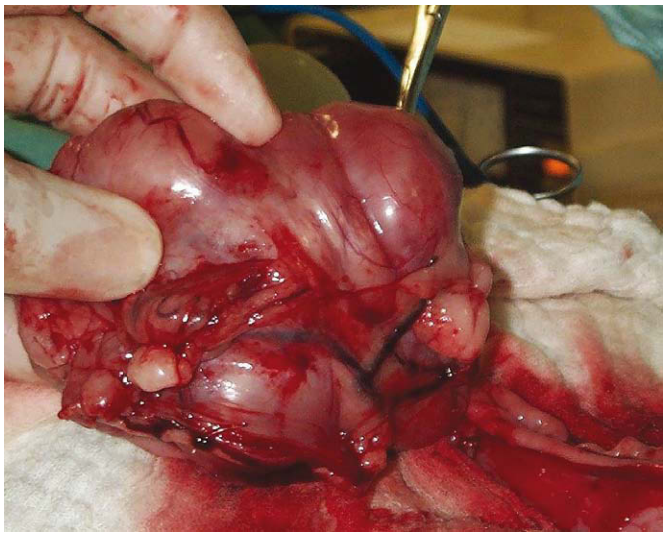

Figure 15.1 Gastric leiomyoma. (Courtesy R Straw.)

result in chronic vomiting and intermittent gastrointestinal (GIT) bleeding. They originate from smooth muscle layers of the stomach wall, can be single or multiple and often occur at the gastro-oesophageal junction. Typical lesions are mucosa-covered masses protruding into the lumen (**Figure 15.1**). Average age is 16 years, so they occur commonly in very old dogs, compared to 10 years for adenocarcinoma.

Surgery is normally curative. As the tumour is benign and occurs in very old dogs, marginal excision is all that is needed. Full-thickness gastric wall resection is unnecessary and contraindicated due to increased risk and morbidity to the patient. The technique of choice is to incise through the stomach opposite the mass, and perform a submucosal resection (Beck & Simpson 1999).

Gastric extramedullary plasmacytomas

These are very rarely seen in the dog. Surgical resection with chemotherapy results in long-term survival (Brunnert et al 1992).

Gastrointestinal mast cell tumours

These tumours have a very poor prognosis with surgery (Ozaki et al 2002).

TUMOURS OF THE SMALL AND LARGE INTESTINES

Canine intestinal tumours

These are uncommon, accounting for approximately 3% of all tumours reported in dogs and 0.6% of all necropsies (Patnaik et al 1977). Intestinal tumours (small and large) account for 92% of all canine non-oral gastrointestinal tumours; 80% of dogs with small intestinal tumours are >7 years old (Gibbs & Pearson 1986).

Sex and breed predilection

Males may be over-represented with intestinal neoplasia (Birchard et al 1986, Couto et al 1989). German Shepherds and collies may be predisposed to non-lymphoid intestinal tumours (Birchard et al 1986, Gibbs & Pearson 1986, Patnaik et al 1977) and Boxers and Shar Peis predisposed to lymphoma (Coyle & Steinberg 2004).

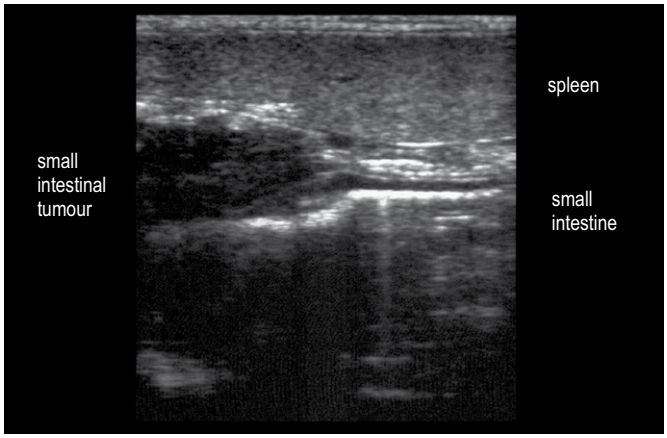

Figure 15.2 Ultrasound scan of a small intestinal tumour.

Feline intestinal tumours

These account for approximately 4–9% of all tumours reported in cats. Intestinal tumours (small and large) account for 68–94% of all feline non-oral tumours (Brodey 1966, Cotchin 1959, Engle & Brodey 1969). Small intestinal tumours are more common in cats (Brodey 1966, Engle & Brodey 1969, Turk et al 1981).

Tumours of the small intestine

Clinical signs

Clinical signs include weight loss, inappetence, intermittent vomiting/diarrhoea, anorexia, bleeding (ulceration – anaemia, hypoproteinaemia, thrombocytopenia), peritonitis (abdominal pain, fever) and malabsorption (intestinal villi filled with neoplastic cells, leading to blocked lymphatics and obstruction).

Diagnostic work-up

Older animals show progressive weight loss and clinical signs of gastrointestinal disease. Anaemia is a common presenting sign characterized by hypochromasia and microcytosis. Hypoglycaemia in leiomyomas and leiomyosarcomas leads to weakness and seizures. In some cases an abdominal mass can be palpated (intestinal tumor or enlarged mesenteric lymph node), in other cases diffuse intestinal thickening with or without enlarged lymph nodes.

Radiography

Radiographs usually reveal an abdominal mass, intestinal accumulation of fluid/gas/ingesta, delayed transit time, mural lesions associated with filling defects, mucosal ulceration or displacement of adjacent bowel loops. Thoracic radiographs rarely demonstrate metastatic disease. Ascites maybe seen secondary to peritonitis.

Ultrasound

Ultrasound is more accurate than radiographs in identifying intestinal masses and at the same time allows evaluation of regional lymph nodes for metastatic disease (**Figure 15.2**). Ultrasound-guided fine needle aspiration (FNA) may be

helpful (Bonfanti et al 2006), although histopathology is often needed for diagnosis.

Biopsy

Endoscopic biopsies are useful for proximal duodenal or rectal tumours, although these may not be diagnostic, even for lymphoma (Couto et al 1989). Laparotomy and biopsy for proximal and distal intestinal tumours is preferred as full-thickness intestinal biopsies are more likely to yield a definitive diagnosis (Kleinschmidt et al 2006).

Canine small intestinal tumours

Most canine small intestinal tumours are malignant.

Lymphoma

The most common intestinal tumour in dogs (and cats) is lymphoma; the majority are multifocal/diffuse and involve the small intestine (large intestine less common). Intestinal lymphoma makes up to 5–7% of all canine lymphomas (Madewell & Theilen 1987), and most are of T-cell origin (Coyle & Steinberg 2004, Miura et al 2004, Steinberg et al 1995). It has been postulated that lymphocytic–plasmacytic enteritis may be a precursor to intestinal lymphoma.

Isolated lesions are treated with surgical excision and adjuvant chemotherapy. Twenty-five per cent of dogs with gastrointestinal lymphoma have involvement of other organs (Chapter 22). Multiple intestinal lymphoma or metastatic disease is best treated by chemotherapy alone (unless there is obstruction or perforation). Diffuse canine alimentary lymphoma does not respond as well to chemotherapy as the multicentric form (Couto et al 1989), although others mention several cases of durable remission with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone)-based protocols. The solitary form does better if it can be surgically removed, with or without adjuvant chemotherapy. Thirty cases of primary canine gastrointestinal lymphoma reported showed a poor prognosis when treated with surgery alone (n = 4), surgery and chemotherapy (n = 8), chemotherapy alone (n = 15) or supportive care alone (n = 3) with a median survival of 13 days, but longer survival for patients with disease of the large intestine (Frank et al 2007).

Adenocarcinoma

The second most common intestinal tumour in dogs (and cats) is adenocarcinoma (**Figure 15.3**), which is commonly annular and in the dog has been reported to have an increased incidence in the large intestine and rectum versus small intestine (Head et al 2002, Patnaik et al 1980). However, another paper reported 71% in small intestine and 29% in large intestine (Paoloni et al 2002).

There are four histological types: solid, acinar, mucinous and papillary (Patnaik et al 1980). They generally have similar biological behaviour, although tumours involving large segments of bowel may be slow growing, with horizontal spread and few metastases, i.e. papillary adenocarcinoma. Acinar, solid and mucinous types tend to show more vertical growth and extend into the wall and other organs.

In dogs, small intestinal adenocarcinomas have a guarded to poor long-term prognosis. They are usually quite advanced at time of diagnosis. Extension of the neoplasm beyond the bowel wall was found in 85% of dogs and 71% of cats at necropsy (Birchard et al 1986). Metastasis is frequently to the regional lymph nodes, especially mesenteric and iliac. Diffuse metastasis to peritoneal surfaces often causes ascites, (carcinomatosis), and carries a grave prognosis. Metastasis is also common to abdominal and thoracic viscera, especially liver, spleen, kidney, myocardium and lungs. The overall median survival time (MST) is 10 months if patients survive the immediate postoperative period. Overall survival time (ST) with metastasis at diagnosis is 3 months, and overall ST without metastasis at diagnosis is 15 months for non-lymphomatous small intestinal masses treated with surgical excision (Crawshaw et al 1998).

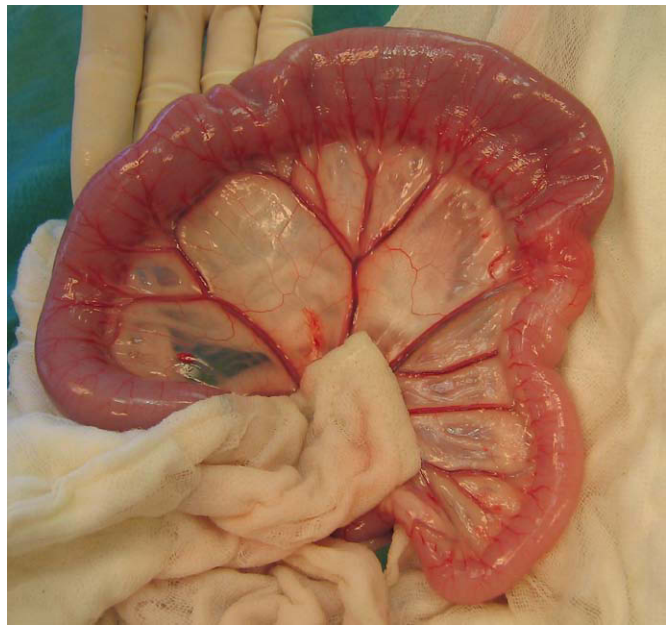

Figure 15.3 Small intestinal carcinoma.

Another paper reported an MST of 233 days (for 6 large intestinal and 15 small intestinal adenocarcinomas) treated with surgical excision. Only gender appeared to influence survival. Female dogs lived a median of 28 days, whereas male dogs lived a median of 272 days (Paoloni et al 2002). The benefits of adjuvant chemotherapy are not known.

Leiomyosarcoma and leiomyoma

In dogs, leiomyosarcomas occur most frequently in the caecum and jejunum. The median age is 12 years. Leiomyosarcomas arise in the outer muscular layers, are nodular, locally invasive and may cause intestinal perforation, but are slow to metastasize (Bruecker & Withrow 1988). Metastasis is often to regional lymph nodes and liver. MST for leiomyosarcoma was 13 months for dogs that survived >2 weeks postoperatively (Kapatkin et al 1992). After excision, 1- and 2-year recurrence-free periods were 80.1% and 67.2% for small intestinal and 83.3% and 61.9% for caecal smooth muscle tumours (leiomyoma and leiomyosarcoma), respectively (Maas et al 2007). Cohen et al (2003) also reported long survival in patients with intestinal leiomyosarcomas (MST of 21.3 months); even dogs with documented metastases had good postoperative survival times (MST of 21.7 months).

Other canine small intestinal tumours

Fibrosarcoma, carcinoids, plasmacytomas and mast cell tumours are rarely reported in dogs.

Extramedullary plasmacytoma

Surgical excision ± melphalan and prednisolone warrant a fair prognosis.

Mast cell tumour (MCT)

MCT of the small intestine is rarely seen and in one published report the MST was 16 days (Takahashi et al 2000). In the authors' experience, long-term survivors have been encountered when the tumour was solitary and no metastasis evident at the time of surgery.

Carcinoids

Found in the duodenum, ileum, colon and rectum, carcinoids arise from enterochromaffin cells in the mucosa. They contain high levels of serotonin and the release of biologically active amines results in 'carcinoid syndrome' (cutaneous flushing, abdominal pain, diarrhoea, dyspnoea). They metastasize to regional lymph nodes and liver.

Treatment

Optimal treatment is wide surgical resection and intestinal anastomosis for solitary malignant intestinal tumours. Margins of 4–8 cm of normal tissue should be taken either side of the mass. En bloc resection (tumour, mesentery and lymph node) may be considered and will give palliative relief even with metastatic disease present. Hepatic and pancreatoduodenal lymph nodes drain duodenum; jejunal lymph nodes drain the jejunum; the ileum is drained by colic and jejunal lymph nodes.

Complications include wound dehiscence resulting in peritonitis and stricture. The potential for tumour recurrence and metastasis depends upon the particular tumour type, as detailed above. Chemotherapy is indicated for diffuse and multicentric lymphoma, and perhaps for solitary intestinal lymphoma after surgery. For more discussion see Chapter 22.

Feline small intestinal tumours

Most feline small intestinal tumours are malignant. The most common is lymphoma, then adenocarcinoma, then mast cell tumour.

Lymphoma (also Chapter 22)

This is the most common feline gastrointestinal tumour. Mean age is 10–12 years. Most (86%) have a palpable abdominal mass (Carreras et al 2003, Mahoney et al 1995). Cats with intestinal lymphomas are usually FeLV-negative using serology, although the role of FeLV and feline immunodeficiency virus (FIV) is uncertain, as many are FeLV positive using polymerase chain reaction (PCR) and immunohistochemistry (IHC) (Jackson et al 1993, 1996). FeLV and FIV status may be more important in Australian cats, with FIV strongly associated and FeLV weakly associated with feline intestinal lymphoma (Court et al 1997, Gabor et al 2001). FeLV status for intestinal lymphoma in cats was prognostic in one study for early stage disease (Mooney et al 1989), but was not prognostic in other studies (Jeglum et al 1987, Zwahlen et al 1998).

Inflammatory bowel disease may be a precursor to intestinal lymphoma in cats (Carreras et al 2003). The proportion of T- and B-cell phenotypes varies, with some reporting predominance of B cell, T cell or neither (Carreras et al 2003, Jackson et al 1996, Zwahlen et al 1998), although immunophenotype does not appear to be a prognostic factor in cats for intestinal lymphoma (Zwahlen et al 1998). In cats, gastrointestinal lymphoma is often part of multicentric disease (80% have multi-organ involvement) (Gabor et al 1998). Metastasis is often to regional lymph nodes, liver and kidneys. Alimentary lymphoma may be diffuse (one-third) or focal (two-thirds).

Treatment is chemotherapy, as surgery does not improve survival compared to chemotherapy alone (Zwahlen et al 1998). The role of surgery is mainly to relieve obstruction, and less commonly to obtain a definitive diagnosis or repair perforation and treat associated peritonitis.

The most significant prognostic indicator is initial response to chemotherapy, with cats that survive the initial induction period generally achieving long-term remission (Richter 2003). Cats that achieve a complete resolution of clinical signs do better (Carreras et al 2003, Malik et al 2001, Milner et al 2005, Zwahlen et al 1998). Patients with the small cell/lymphocytic form have a better prognosis than those with the lymphoblastic form (see below) (Fondacaro et al 1999).

Clinical stage, intestinal site or extent of intestinal involvement was not prognostic in one paper (Mahoney et al 1995). In a series of cats with lymphoma of various anatomical sites treated with chemotherapy, anatomical site, sex, age and clinical stage did not influence the duration of first response or survival time, but those that had a complete remission after initial treatment lived longest (MST of 654 days vs. 122 days) (Milner et al 2005). The overall median duration of first remission was 20 weeks, and overall MST was 40 weeks in 21 cats treated with combination chemotherapy (Zwahlen et al 1998). In 28 cats with alimentary lymphoma treated with chemotherapy, the median survival time was 50 days. However, about 30% of these cats achieved complete remission, ranging from 30 to 1700 days (median 213 days) (Mahoney et al 1995).

Subsets of feline intestinal lymphoma

- Lymphocytic/small cell: low grade
- Lymphoblastic: high grade

When treated with chemotherapy, small cell/lymphocytic intestinal lymphoma had a 69% complete remission rate for about 2 years compared to only 18% for <3 months' duration for the lymphoblastic form. Lymphoblastic intestinal lymphoma was more likely to cause a palpable abdominal mass and require surgery for obstruction than lymphocytic (Fondacaro et al 1999).

Epitheliotropic intestinal lymphoma

This type of lymphoma is mostly T cell, and may be a continuum of feline inflammatory bowel disease. Five of nine cats with epitheliotropic intestinal lymphoma treated with chemotherapy were long-term responders, with an MST of 11 months; the other four responded poorly and were euthanized within 3.5 months (Carreras et al 2003).

Globule leucocyte tumour/large granular lymphocyte lymphoma

This form is characterized by large mononuclear cells with prominent azurophilic granules. Diffuse metastasis at diagnosis is common, and often rapidly progressive and fatal, although individual cases may do well with surgery (McPherron et al 1994).

Adenocarcinoma

This accounts for 20–35% of all feline gastrointestinal tumours (Cribb 1988) and 0.4–2.9% of all cat malignancies. Mean age is 11 years with Siamese cats predisposed. There is no association with FIV or FeLV. Adenocarcinoma tends to be found in small intestine, especially jejunum or ileum (Cribb 1988, Patnaik et al 1976). Histological subtypes include tubular, undifferentiated and mucinous (Turk et al 1981). Tubular may have a better prognosis (Cribb 1988). Most are advanced, with metastasis in 72% of cases at diagnosis (Kovosky et al 1988). Metastasis is to abdominal serosa (carcinomatosis), lymph node, liver and lungs.

Osteochondroid metaplasia has been reported (Turk et al 1981) and generally appears as firm, annular, constrictive masses; it is annular when the lumen is constricted 360 degrees and intraluminal when tumour spreads into the lumen as well as infiltrative into the wall.

Kosovsky et al (1988) reported on 23 cats with small intestinal adenocarcinoma that were treated with resection and anastomosis. Eleven died or were euthanized within 2 weeks, 12 survived an average of 15 months (1.5–30 months). Of these 12, 5 cats with known lymph node involvement survived a mean of 12 months, and 2 cats with omental carcinomatosis lived 4.5 and 28 months. In another study, the MST was 2.5 months when treated with resection and anastomosis (Cribb 1988). Cats given no treatment survived for 2 weeks (Birchard et al 1986, Kosovsky et al 1988).

Mast cell tumour (MCT)

This is the third most common feline gastrointestinal tumour after lymphoma and adenocarcinoma. Cats are more frequently affected than dogs. Mean age is 13 years. MCT more commonly involves the small intestine with equal distribution between duodenum, jejunum and ileum, and <15% colonic involvement. Peritoneal effusion is relatively common. Peripheral mastocytosis and eosinophilia are rare (unlike the splenic form). Peripheral eosinophilia has been reported in two cats (Bortnowski & Rosenthal 1992). Cytology of peritoneal effusion is often diagnostic. There is no association with ulceration (this is more likely in the systemic form).

Metastasis is common and sites include mesenteric lymph nodes and liver, and less commonly spleen and bone marrow. Histologically they are generally poorly differentiated with less prominent cytoplasmic granules. Prognosis is poor, as they do not respond to chemotherapy and most die soon after diagnosis (Howl & Petersen 1995). Anecdotally, solitary intestinal MCT without metastasis may have prolonged survival following end-to-end anastomosis.

Leiomyoma and leiomyosarcoma

These tumours are rare in cats.

Duodenal adenomatous polyps

Mean age is 12 years, 83% male castrated, Asian cats may be over-represented.

Clinical signs include acute and chronic vomiting with haematemesis, and anaemia has been reported in 50% of cases. Surgical resection and end-to-end anastomosis was curative in 15 of 18 cats that survived >2 weeks postoperatively (11 alive, 3 dead of unrelated causes and 1 lost to follow-up) (MacDonald et al 1993).

Carcinoids

Rare in the cat, carcinoids are occasionally seen in the duodenum or ileum. They arise from enterochromaffin cells in the mucosa. They contain high levels of serotonin and the release of biologically active amines results in 'carcinoid syndrome' (cutaneous flushing, abdominal pain, diarrhoea, dyspnoea). They metastasize to regional lymph nodes and liver.

Tumours of the large intestine

Clinical signs

These can include tenesmus, haematochezia, dyschezia, rectal bleeding not associated with defecation, rectal prolapse or increased frequency of defecation. Other signs include vomiting, diarrhoea and weight loss. Collapse and septic peritonitis with perforation is also possible. Debilitation and hypoproteinaemia may complicate treatment.

Diagnostic work-up

Abdominal palpation demonstrates a palpable abdominal mass and pain; rectal examination usually reveals a lesion/stricture. Proctoscopy will allow visualization of tumours and in many cases a biopsy can be obtained by proctoscopy.

An abdominal mass, abdominal effusion, filling defect, etc. may be seen using radiographs ± contrast study. Care should be taken if perforation is suspected as barium is very irritant (iodine is preferred). Thoracic radiographs rarely identify pulmonary metastasis.

Surgery provides the definitive diagnosis.

Canine large intestinal tumours

Adenomatous polyps

These are the most frequently reported tumours of the canine rectum (**Figure 15.4**) (Holt & Lucke 1985). Haematochezia was the most common (82%) presenting sign in 34 dogs with colorectal adenomatous polyps or carcinoma in situ (Withrow 1997). Most of these dogs presented with a solitary rectal mass. Recurrence of clinical signs after surgery was common (41%), and malignant transformation of the tumour was documented in 18% of cases. Local recurrence and malignant transformation occurred more often if multiple masses, diffuse disease or carcinoma in situ was initially diagnosed (Valerius et al 1997). Malignant transformation was also reported in three of five dogs, two of which suffered local recurrence at 16 and 24 months, and the third died of unrelated causes 5 months after surgery (Danova et al 2006), and in an earlier study in one of five dogs (White & Gorman 1987).

Adenomatous polyps of the distal colon and rectum can be treated surgically by pedicle ligation or excision with clean

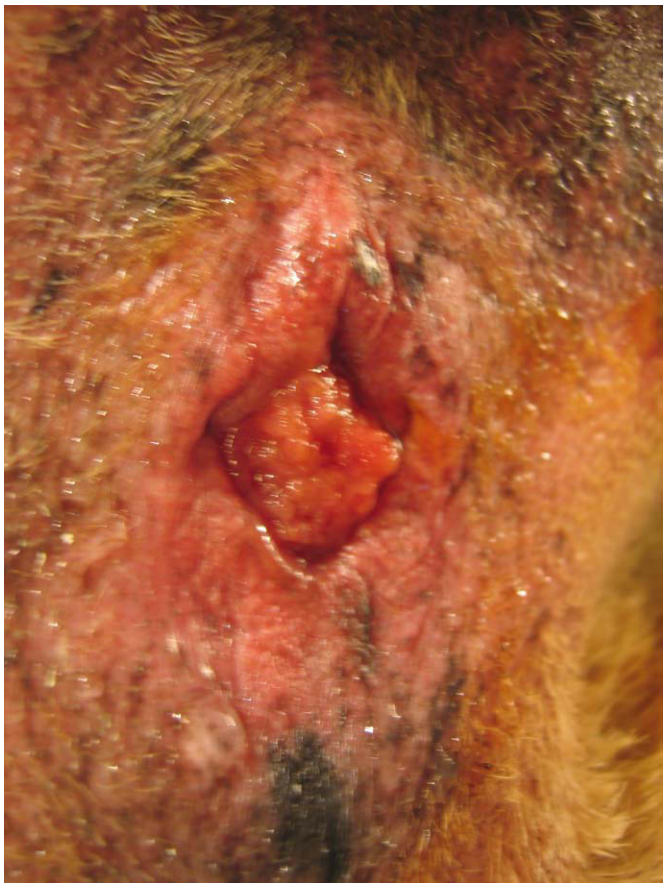

Figure 15.4 Rectal polyp.

margins, electrocautery, cryosurgery, transanal endoscopic treatment or piroxicam. Proctoscopy is ideal before surgical treatment as multiple polyps/masses may be present, and this will influence treatment and prognosis.

Medical management with oral or suppository piroxicam for 4–6 weeks showed a good to excellent response in seven of eight dogs with rectal polyps (Knottenbelt et al 2000). This treatment has the advantage of avoiding the need for surgery and its associated complications (e.g. dehiscence, peritonitis, stricture), although long-term follow-up and survival was not reported. Such palliative treatment may be an appropriate choice for many clients, but they should be aware that if tumour remains, there is the persistent potential for malignant transformation and, as a consequence, possible tumour-related morbidity or fatality.

Distal pedunculated lesions can be exteriorized and ligated at the base, avoiding a full-thickness rectal wall resection, but follow-up to monitor closely for recurrence (rectal palpation ± proctoscopy) is desirable, particularly if malignant transformation is detected histologically.

Full-thickness rectal wall resection of two distal rectal polyps (with histological characteristics of malignant transformation) with 1 cm 'clean' margins resulted in local recurrence after a prolonged period (16–24 months) and recurrent (malignant) disease was again treated surgically to result in further prolonged survival (14–86 months) (Danova et al 2006).

Holt & Lucke (1985) reported no recurrence in 14 of 15 dogs with rectal polyps treated with surgery (n = 14) or cryotherapy (n = 1). Four of five dogs with distal rectal polyps treated by exteriorization and resection with 1 cm margins (via anal approach) had long-term survival (17–84 months), the other was lost to follow-up (Danova et al 2006). Prolonged survival (1–5 years) with rare tumour-related deaths was also reported for 17 dogs treated surgically for rectal polyps (Seiler 1979).

The best candidates for surgery are dogs with more distal, smaller lesions. In the authors' experience, small polyps are better treated surgically (resection with clean margins) rather than medically. One reason is that malignant transformation and local recurrence are more likely once lesions are >1 cm in diameter (Seiler 1979). Another is that superficial biopsies or gross polypoid appearance unfortunately do not reliably differentiate malignant from benign. Smaller lesions are also more amenable to curative excision without complication (less tension on repair, healthy margins of normal tissue for closure, better exposure, etc.).

Larger lesions, lesions with 360-degree involvement, and lesions sited more cranially (e.g. intrapelvic rectum) are more difficult to excise with clean margins and serious surgical complications are more of a concern (e.g. dehiscence and peritonitis, stricture, faecal incontinence, local recurrence). Larger and recurrent polyps are more likely to have undergone malignant transformation (Seiler 1979).

Surgical approaches for distal lesions include an anal approach (rectal), dorsal approach or 'inverted U', and rectal pull-through. Mid to proximal rectal lesions are better approached surgically via pelvic osteotomy, and intra-abdominal colonic tumours with an exploratory celiotomy. Faecal incontinence is expected if there is permanent damage to the nerves of the peritoneal region with surgery (generally this occurs with resection of lesions >4–6 cm proximal to the anus) or to both branches of the caudal rectal nerve innervating either side of the anal sphincter.

In 2007, Holt reported 13 dogs with extensive rectal neoplasia, considered inoperable by conventional surgical techniques, treated by transanal endoscopy. Tumours affecting different lengths of rectal mucosa, varying from 2 to 13 cm and 25–100 % of the rectal circumference, were diagnosed as benign on biopsy. Treatment was curative in five dogs, palliative in three and associated with a poor result in the remaining five. Complications of the technique included rectal perforation, leading to peritonitis and death.

Ideally, malignant disease should be treated with excision with clean margins where possible. Palliative (transanal endoscopic treatment or piroxicam) rather than curative (surgical excision of all local tumour) treatment may be undertaken, depending on the experience and skill of the surgeon, the quality of life of the patient with medical management (i.e. unresolved haematochezia, tenesmus, diarrhoea, etc.), patient age and the expectations of the client.

Adenocarcinoma

Adenocarcinoma of the large intestine in dogs usually has a different biological behaviour than small intestinal adenocarcinoma, and carries a more favourable prognosis. The colon and rectum are more common sites for adenocarcinoma than the small intestine in dogs (Head et al 2002, Patnaik et al 1980). The rectum is a more common site than the colon,

with about 50% of 78 cases occurring in the mid-rectal area (Church et al 1987).

Large intestinal adenocarcinoma in dogs tends to have a low incidence of local invasion and is slow to metastasize. In 23 dogs with large intestinal adenocarcinoma, treated only with faecal softeners, a mean survival of 15 months was reached. However, this was improved to 22 months when treated with local excision. Most of these 78 dogs were euthanized due to severity of clinical signs caused by local disease rather than metastasis. Dogs with single polypoid adenocarcinomas had mean survival of 32 months, those with nodular or cobblestone lesions had mean survival of 12 months, and those with annular strictures had survival of 1.6 months (Church et al 1987).

Danova et al (2006) reported 14 dogs with adenocarcinoma (n = 8), carcinoma (n = 5) or mucinous carcinoma (n = 1) of the rectum treated via exteriorization of the mass from an anal approach (rectal prolapse) and resection with 1 cm margins of grossly normal tissue. Lesions were 2.5–5 cm proximal to the anus and ranged from 0.6 to 14.7 cm^3 in volume. Permanent faecal incontinence did not occur in any dog. Only the mucinous carcinoma was incompletely excised, and euthanasia for unrelated reasons occurred after 38 months. The disease-free interval for 12 of 14 dogs followed ranged from 14 to 84 months (mean of 34 months). Metastasis to sublumbar lymph nodes was not identified in any of the dogs with various rectal tumours, even at necropsy (Danova et al 2006).

Fifty per cent of large intestinal adenocarcinomas are associated with annular constrictions. Diffuse infiltration of the entire large bowel has also been reported (Prater et al 2000).

The surgeon must consider control of dyschezia and haematochezia as major goals. Surgical approaches are as for rectal polyps. There is one report of an incontinent end-on colostomy after failed rectal pull-through for an annular rectal adenocarcinoma in a dog, which survived 4 months with mild peristomal dermatitis as the only complication (Kumagai et al 2003). Of 11 dogs undergoing cryosurgery, nine (82%) had complications including rectal prolapse, stricture, perineal hernia and recurrence.

Orthovoltage radiation therapy for rectal adenocarcinoma was described as an alternative to surgery where six of seven dogs experienced complete regression of their tumour (rectum everted to allow exposure). Tumour control was 46% at 1 year and 67% 1-year survival (Turrell & Théon 1986).

There is no proven benefit of adjuvant chemotherapy in dogs (or cats). In dogs, failure is usually from recurrence of local disease rather than distant metastasis. In the event that local disease is controlled, adjuvant chemotherapy may prove beneficial for prolonging survival.

Colorectal leiomyomas and leiomyosarcomas

Median age for diagnosis of these tumours is 12 years and they are seen most frequently in medium/large breed dogs. Removal is by blunt dissection from the wall with good overall survival times (MST 26 months) (McPherron et al 1992). Caecal leiomyomas were reported to have an MST of 28 months (Gibbons & Murtaugh 1989), and caecal leiomyosarcomas an MST of 7.5–31 months (Kapatkin et al 1992), indicating an excellent prognosis following surgery.

Clinical signs of tenesmus and ribbon-like stools reflect extraluminal compression. Haematochezia is absent due to lack of mucosal involvement.

Plasmacytoma

Rarely reported, patients can expect a good prognosis with surgical resection (Danova et al 2006) and surgical resection with adjuvant chemotherapy (Trevor et al 1993).

Lymphoma

Lymphoma occurs infrequently in the large intestine. Two cases of rectal lymphoma had encouraging results after surgical excision (Frank et al 2007, Holt & Lucke 1985). For patients not considered candidates for surgery, radiotherapy or chemotherapy should be considered.

Feline large intestinal tumours

In cats, the most common large intestinal tumour is adenocarcinoma, followed by lymphoma and mast cell tumour.

In one study (Slawienski et al 1997), the mean age was 12.5 years; 46% were adenocarcinoma, 41% lymphoma, 9% mast cell tumour and 4% neuroendocrine carcinoma. Cats with tumours of colon, caecum and ileocolic junction were included, but not rectal. For cats with adenocarcinoma, those treated with subtotal colectomy had an MST of 138 days compared to 68 days for mass resection. Obtaining clean margins increased survival time; however, metastases at time of surgery decreased survival. About 80% of cats with adenocarcinomas had metastasis (local or distant). Cats with negative lymph nodes at surgery lived a median of 259 days, versus 49 days if positive. Four cats with adenocarcinoma were treated with doxorubicin, and lived a median of 280 days versus 56 days without.

Metal stents placed under fluoroscopy were palliative in two cats with colonic adenocarcinoma, one for 274 days (with good quality of life and euthanasia due to eventual distant metastasis) and one for only 19 days (euthanasia due to perceived reduction in quality of life) (Hume et al 2006).

About 30% of cats with lymphoma had distant metastasis, and about 10% had local metastasis. Cats with lymphoma had an MST of 97 days with chemotherapy versus 100 days without. A difference in survival based on surgical approach was not seen (Slawienski et al 1997), and the site of intestinal involvement for lymphoma in cats was not prognostic (Mahoney et al 1995, Zwahlen et al 1998).

Of four cats with mast cell tumour, two had local metastasis – one distant, one unknown. The median survival was 199 days. All were treated with surgery and prednisolone (Slawienski et al 1997).

Of the 46 cats in this study, 39 died from tumour, 5 were alive, 2 were lost to follow-up. Overall, cats with subtotal colectomy had significantly increased survival over those with mass resection. Cats with metastasis had a median survival of 49 days, and 259 days without metastatic disease. Those treated with chemotherapy had an MST of 280 days compared to 56 days without. Those treated with colonic resection had a MST of 198 days versus 22 days for medical management. Metastasis was local in 24% and distant in 39% (Slawienski et al 1997).

These cats may benefit from radiation therapy of local disease, but there are no reports of this as yet.

Perianal tumours

Perianal adenomas (circumanal, hepatoid, sebaceous)

These are benign tumours, common in older intact male dogs, rare in female dogs. They are not reported in cats as cats have no glands analogous to canine perianal sebaceous glands. Adenomas comprise 80% of all perianal tumours, and are the third most common tumour in male dogs. They occur four to five times more commonly than carcinomas, and are more common in the Cocker Spaniel, Beagle, Bulldog and Samoyed (Wilson & Hayes 1979). Older intact male dogs are at greater risk for developing adenomas, and castration results in regression of the tumour (Wilson & Hayes 1979). There is a higher incidence of associated testicular interstitial tumours with adenomas, suggesting testosterone production is involved (Wilson & Hayes 1979).

Perianal adenomas in females occur in ovariohysterectomized dogs where oestrogen does not suppress the tumour. There is one report of a spayed bitch with pituitary-dependent hyperadrenocorticism causing hypertestosteronaemia and perianal adenomas (Dow et al 1988).

Clinical signs

Slow growing non-painful mass(es), present for months to years, are the usual presenting signs. They may be single, multiple or diffuse. They are usually located on the hairless skin of the anus but can also develop on prepuce, scrotum or tail base. They may become very large, ulcerated and infected; rarely are they fixed to deeper tissues (**Figure 15.5**). They are usually <3 cm, well circumscribed, and elevated from the perineum.

Diagnostic work-up

Fine needle aspiration does not easily differentiate adenoma from adenocarcinoma, although it is useful to rule out other disease. 'Hepatoid' terminology comes from a similar appearance to hepatocytes. Biopsy is needed to definitively differentiate malignant from benign.

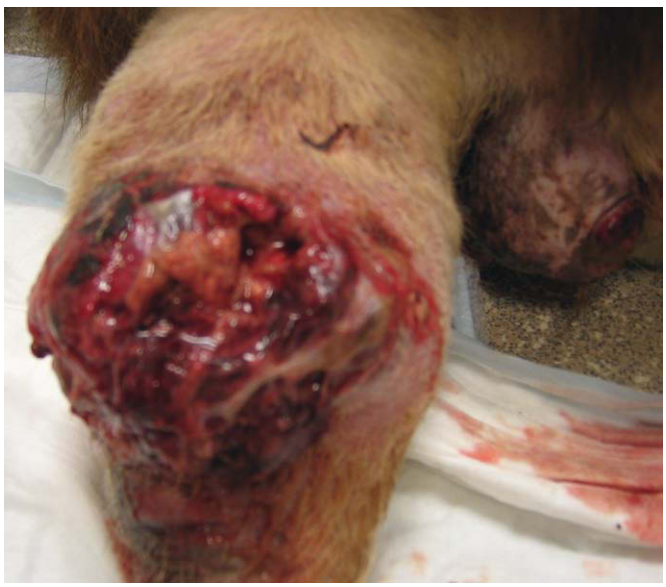

Figure 15.5 Large perianal adenoma.

Treatment

For larger lesions, where surgery would be difficult or risky, castration alone should be performed first to shrink the tumour and make it more amenable to surgery in the following weeks to months. Smaller lesions should be treated with castration and removal with minimal margins. Over 90% of male dogs are cured with castration and mass removal (Nielson & Aftosmis 1964, Wilson & Hayes 1979). In female dogs, perianal adenomas should be removed with minimal margins. Screening for hyperadrenocorticism may be prudent in female dogs with perianal adenomas. In all cases, perianal tissue should be submitted to histopathology to confirm the diagnosis.

Perianal adenocarcinoma (circumanal, sebaceous)

Clinically, these may look similar to perianal adenomas, but grow faster, and are often ulcerated and adherent/infiltrative into deeper tissues. They are much less common than adenomas in dogs, and are not reported in cats. Large breed male dogs are over-represented (Vail et al 1990).

Adenocarcinomas occur in intact and neutered males and female dogs, implying no hormonal influence (Vail et al 1990, Wilson & Hayes 1979). Perianal adenocarcinomas do not respond to castration. Aggressive surgery with adequate margins (2–3 cm) is required; 50% or more of the anal sphincter can be removed without permanent faecal incontinence (Withrow 2001**)**. The nerve supply to the anal sphincter (caudal rectal nerve) must be intact on at least one side to maintain faecal continence. Metastasis is seen in 15% at diagnosis (Vail et al 1990). Regional lymph node metastasis can be excised in >50% of cases (Withrow 2001). Tumours <5 cm do well; recurrence is common but may take many months, and several surgeries can be done. Emergence of distant or regional metastasis may take many years (Vail et al 1990).

If excision of the primary is not possible, radiotherapy is effective at local control.

Anal sac gland carcinoma (ASGC)

ASGC is a malignant tumour arising from the apocrine secretory epithelium in the wall of the anal sac. It accounts for 17% of perianal tumours in dogs (Berrocal et al 1989). Cats have been reported with this tumour, although it is very uncommon (Chun et al 1997, Mellanby et al 2002). Historically, this tumour was thought to predominate in older female dogs; however, more recent studies have shown that males and females are at about equal risk for developing this tumour (Bennett et al 2002, Polton & Brearley 2007, Williams et al 2003). English Cocker Spaniels are over-represented and often have a younger age of onset (Polton 2006, 2007).

Approximately 30–50% of dogs with ASGC present with paraneoplastic hypercalcaemia and the clinical signs of polyuria/polydipsia (PU/PD) may be the presenting complaint (Bennett et al 2002, Williams et al 2003). Metastasis is present in 50–80% of cases at the time of diagnosis (Bennett et al 2002, Goldschmidt & Zoltowski 1981, Ross et al 1991, Williams et al 2003).

Clinical signs

Clinical signs include tenesmus and/or straining to urinate, flattening of stools, PU/PD, a visible lump adjacent to the anus and anorexia. Hind limb paresis/lameness and spinal pain is also reported (Brisson et al 2004).

Diagnostic work-up

For patients presenting with PU/PD, routine blood work revealing elevated calcium would direct the clinical investigation for a possible anal sac tumour.

Rectal examination

Rectal examination usually reveals a hard firm mass within the anal sac. Primary tumours can be small, with significant metastatic disease, or large with or without metastases. The medial iliac/sub-lumbar lymph nodes should be checked for enlargement by rectal and abdominal palpation. If a lump is felt in either anal sac, a fine needle aspirate can be taken, depending on the size of the tumour.

Biopsy

Biopsy prior to definitive surgical resection is usually unnecessary in the authors' opinion, as clinical examination and cytology are highly suggestive. Wide margins are not possible due to proximity to the rectum, and excision needs only to be beyond the anal sac wall/capsule. If the tumour has already extended beyond the wall/capsule of the anal sac, the widest possible margins are taken, although it is very difficult to ensure wide clean margins in this location. If a biopsy is taken prior to definitive surgical resection, a wedge biopsy is preferred over a tru-cut biopsy. This is because the entire biopsy tract must be removed en bloc with the tumour at surgery, and the extent of the previous biopsy tract is easier to define after a wedge biopsy. Tru-cut biopsy needles often go through the anal sac capsule on the deep aspect, especially for smaller tumours, potentially disseminating cancer cells locally and compromising later attainment of clean margins and local disease control. Benign anal sac tumours are very rare; the vast majority are malignant (Emms 2005).

Radiography

Abdominal radiographs may show increased size of sub-lumbar lymph nodes with advanced disease. Extension of metastatic tumour into the spine can occur, causing vertebral bone lysis (Brisson et al 2004). Thoracic radiographs are indicated prior to surgery for staging purposes in all patients, as metastatic disease may uncommonly 'skip' the abdomen and be evident in the lungs. Finding a solitary pulmonary nodule may be consistent with a concurrent primary lung tumour and is therefore not definitive for metastasis.

The presence of early pulmonary metastatic disease is not an absolute contraindication to surgery, as it is generally subclinical. Most normocalcaemic dogs are clinically well, except for clinical signs caused by local tumour (straining etc.), which is addressed by removal of the primary mass. Distant metastatic disease may take months to progress.

Ultrasound

Abdominal ultrasonography is preferred over radiography for staging of the abdomen as it is more sensitive in detecting lymph node enlargement and assessing the liver, a preferred secondary site. However, many older dogs will have nodular hyperplasia of the liver and the presence of liver nodules on ultrasound is not conclusive of malignancy; this must be based on a biopsy.

Advanced imaging of abdomen (e.g. contrast-enhanced CT/MRI) is very useful to predict whether or not resection of enlarged regional lymph nodes is feasible. Unfortunately, this is something that may only be known for certain at surgery.

Treatment

Surgery

Prompt anal sacculectomy is advised for treatment of the primary tumour(s). If hypercalcaemia of malignancy is present, removal of the inciting cause, i.e. the tumour (primary and metastases, if possible), is required to normalize serum calcium. The patient should be stable enough to undergo general anaesthesia, and surgery should not be unnecessarily delayed. Care should be taken not to perforate the rectum during dissection, and if there is bilateral disease (Emms 2005), to preserve the innervation to the anal sphincter. As mentioned before, 50% or more of the anal sphincter can be removed without concern of permanent faecal incontinence.

Enlarged regional lymph nodes (based on abdominal ultrasound) should be excised at the time of removal of the primary mass via an exploratory celiotomy (**Figure 15.6**). The surgeon should digitally palpate the entire pelvic canal and sub-lumbar area as there is often a chain of enlarged lymph nodes, especially in advanced disease. Removal of sub-lumbar lymph nodes is not necessarily an easy surgery; some will 'shell out' nicely with finger dissection, others are deeply attached and invasive to critical regional structures such as vena cava, aorta, internal iliac vessels and nerves of the pelvic plexus. The smaller the lymph nodes, the easier they are to remove, and so even if they are not causing any clinical signs at the time of removal of the primary tumour, it is better to get them out early. Once these nodes are very large, removal may be very difficult, and radiotherapy and chemotherapy may be a better option for palliation (Bley et al 2003, Turek et al 2003).

Incising the capsule of the lymph node and removing its contents is a useful method of debulking and palliation in some cases. There is one case report of a cystic lymph node that was incised, drained and omentalized to palliate clinical signs of tenesmus and dysuria for 18 months (Hoelzler et al

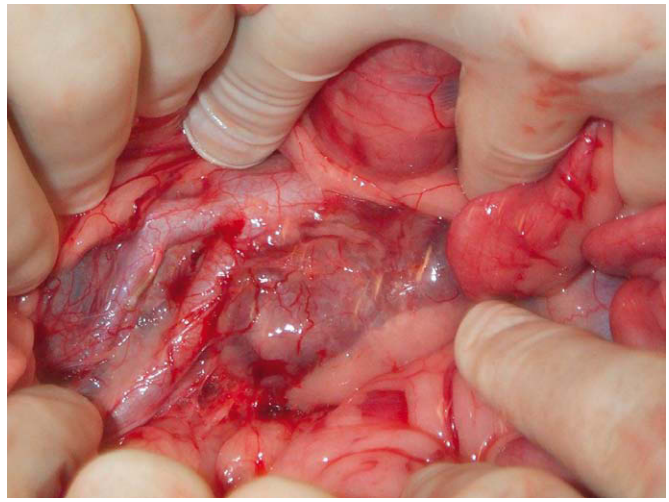

Figure 15.6 Metastatic lymph nodes from an anal sac gland carcinoma. (Courtesy R Straw.)

2001). An experienced surgeon may need to assess resectability or ability to debulk enlarged lymph nodes intraoperatively, and as mentioned above, three-dimensional imaging can be helpful. Surgery to remove very large and invasive intra-abdominal metastatic disease is usually a last-ditch attempt at palliation, involving significant risk to the animal of intraoperative haemorrhage and postoperative neurological dysfunction (e.g. incontinence, hind limb paresis). One paper reported five dogs treated with surgical debulking of metastatic anal sac adenocarcinoma, with no surgical complications. Three dogs were euthanized with an MST of 20.6 months, one dog was alive for 19 months, and one dog had five sequential surgical procedures (one iliac lymphadenectomy and four debulking procedures of metastatic neoplastic tissue around and dorsal to the iliac vessels extending into the pelvic cavity) and was living 54 months after the initial surgery (Hobson et al 2006).

Chemotherapy

Although various agents have been tried for adjunctive or palliative therapy, efficacy is not well established, e.g. carboplatin, cisplatin (Bennett et al 2002), melphalan (Emms 2005) and mitoxantrone (Turek et al 2003). The authors recommend carboplatin for patients with minimal disease; however, for patients with advanced disease radiotherapy is more likely to be effective in 'shrinking' large tumours.

Radiotherapy

If excision of the primary tumour is incomplete, then adjuvant radiotherapy may be considered to reduce the likelihood of local recurrence. Side effects include local inflammation, radiation-induced colitis and stricture. Palliative radiotherapy and chemotherapy will reduce the size of inoperable metastatic lymph nodes (**Figure 15.7**) (Bley et al 2003, Turek et al 2003).

Prognosis

The best prognosis is expected for patients with small tumours that are completely excised and no detectable regional lymph node or distant metastasis at the time of presentation. In these cases, surgery has a better chance of removing all local tumour, and the progression of clinically significant metastatic disease generally occurs slowly, with eventual recurrence of clinical signs (e.g. faecal tenesmus and/or dysuria or hypercalcaemia). The pelvic outflow obstruction-free interval and thus survival is greatly prolonged if lymph nodes are removed, even multiple times (Hobson et al 2006), especially before they are large enough to cause significant surgical risk or complication to the animal. The survival time of dogs without lymph node metastasis is not significantly different from the survival time of dogs with lymph node metastasis, if treated with surgical removal of the primary tumour and enlarged lymph nodes, and adjuvant chemotherapy (Emms 2005).

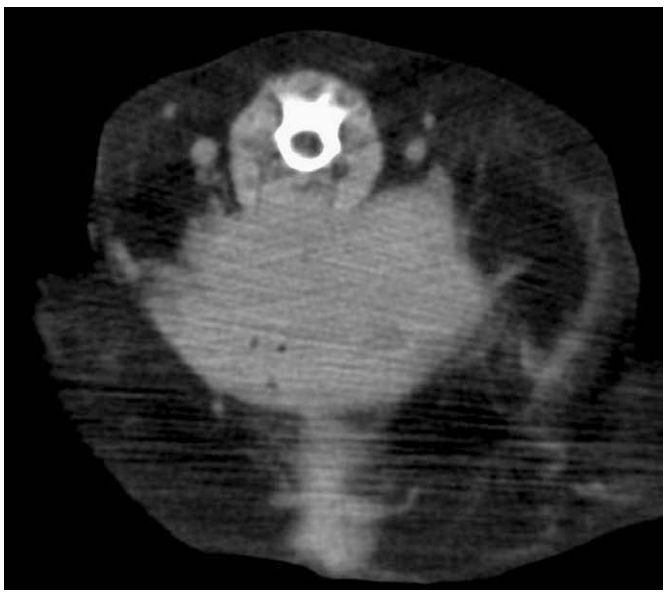

Figure 15.7 CT of a dog with large sub-lumbar lymph nodes from an anal sac gland carcinoma.

Multimodal therapy appears to be optimal, as 15 dogs treated with combination therapy (surgery, radiation and chemotherapy) had a median survival of 31 months in one study (Turek et al 2003). The median survival of 104 dogs treated with surgery, radiation or chemotherapy, or multimodal, was 544 days (Williams et al 2003).

Negative prognostic factors for survival include lack of treatment (Polton & Brearley 2007), and treatment with chemotherapy alone (MST 212 days) compared to other treatments (MST 584 days) (Williams et al 2003). Treatment not involving surgery lead to an MST of 402 days compared to 548 days for dogs that had surgery as part of their treatment (Williams et al 2003).

Large size of the primary tumour was a negative prognostic factor (Polton & Brearley 2007, Williams et al 2003). Patients with primary tumours 10 cm^2 or larger had shorter MST (292 versus 584 days) (Williams et al 2003).

The presence of lymph node metastases is a negative prognostic factor (Polton & Brearley 2007, Ross et al 1991), but regional lymph node metastasis did not correlate with a poorer prognosis if those nodes were removed (Emms 2005). Lymph node extirpation was a statistically significant positive prognostic indicator by bivariate analysis (Polton & Brearley 2007). Lymphadenectomy has been shown to provide long-term survival to a series of five patients with metastatic anal sac adenocarcinoma, with one dog surviving 54 months after initial surgery (Hobson et al 2006).

Distant metastasis is a negative prognostic factor (Polton & Brearley 2007). Dogs with pulmonary metastasis had significantly shorter survival than dogs without (MST 219 versus 548 days) (Williams et al 2003).

Hypercalcaemia is a negative prognostic factor in some studies (Ross et al 1991, Williams et al 2003) but not others (Bennett et al 2002, Polton & Brearley 2007).

Young age at the time of diagnosis, especially in English Cocker Spaniels, is also a negative prognostic factor.

For many patients, these tumours are not detected until they are very large and routine rectal examination on dogs over 5 years of age would undoubtedly lead to some of these tumours being detected earlier. Early detection of any cancer is desirable as improved survival times are likely and certainly morbidity from surgery would be significantly reduced. In terms of facilitating early detection of this malignancy there is little excuse for not performing routine checks.

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Tumours of the hepatobiliary system and exocrine pancreas

Hepatic tumours are rare, accounting for about 1% of canine and 2% of feline neoplasms. Average age is 10 years (Liptak 2007). There is no known breed or sex predisposition. Aetiology is unknown, although exposure to aflatoxins (Hammer & Sikkema 1995), radiation and various chemical carcinogens (diethylnitrosamine, dichlorobenzidine, aramite, 3-acetylaminofluorene and others) has been shown to induce them (Thamm 2001). Metastatic liver tumours are much more common than primary tumours (perhaps due to dual afferent blood supply from the portal vein and hepatic artery) (Hammer & Sikkema 1995). These most commonly arise from the gastrointestinal tract, splenic haemangiosarcoma, pancreatic tumours, mammary adenocarcinomas and anal sac adenocarcinomas.

Canine hepatic tumours

There are three morphological types of hepatobiliary tumour: massive, nodular and diffuse.

1. *Massive*: Solitary, large. Metastatic rate is variably reported but generally low (Liptak et al 2004, Patnaik et al 1980). Confined to one liver lobe (especially left) (Patnaik et al 1980). Most commonly hepatocellular carcinomas, but can also be biliary carcinomas or sarcomas (Liptak 2007).
2. *Nodular*: Multifocal disease usually involving multiple lobes, typically sarcomas, carcinomas, or carcinoids (Liptak 2007). Nodular hyperplasia is a benign condition seen in older dogs and is a major differential for nodular hepatic disease. Focal hepatic lesions in dogs using ultrasound were diagnosed as nodular hyperplasia in 25% and 36% of cases (Cuccovillo & Lamb 2002, Vörös et al 1991).
3. *Diffuse*: May represent a late stage of tumour development when coalescing nodules cause effacement of hepatic lobe parenchyma. This is primarily seen with carcinomas and carcinoids (Liptak 2007).

Feline hepatic tumours

The primary hepatobiliary tumours seen in cats are bile duct adenomas and carcinomas, hepatocellular adenomas and carcinomas, hepatoblastomas and myelolipomas. The most common secondary liver tumour is lymphoma (Neiger 2003a). Pancreatic, intestinal and renal tumours not uncommonly metastasize to the liver in cats.

Primary hepatobiliary tumours in cats are more commonly benign than malignant. Biliary adenomas account for >50% of all hepatobiliary tumours in cats (Adler & Wilson 1995, Lawrence et al 1994, Patnaik 1992, Post & Patnaik 1992). Hepatocellular tumours are less common than biliary tumours. Bile duct carcinoma is the most common malignant primary tumour (Lawrence et al 1994, Patnaik 1992, Post & Patnaik 1992) and hepatocellular carcinoma is the second most common (Cullen & Popp 2002, Hammer & Sikkema 1995, Lawrence et al 1994, Patnaik 1992, Patnaik et al 1980, Post & Patnaik 1992, Thamm 2001). Bile duct carcinoma is generally aggressive, with diffuse intra-abdominal metastasis and carcinomatosis in 67–80% of cases (Lawrence et al 1994, Patnaik 1992, Post & Patnaik 1992).

Gall bladder tumours are <5% of biliary carcinomas in cats and dogs (Hayes et al 1983, Patnaik 1992, Patnaik et al 1981a). Biliary carcinomas may be intra- or extrahepatic, with no clear predominance of either location (Lawrence et al 1994, Patnaik 1992). Cats with malignant liver tumours have a poor prognosis, with 86% of the cats dying or being euthanized during hospitalization (Lawrence et al 1994).

Paraneoplastic alopecia has been reported in one cat with hepatocellular carcinoma (Marconato et al 2007). A hepatic abscess was found secondary to hepatocellular carcinoma in another cat (Singh et al 2005). Benign liver tumours in cats have a good prognosis with partial or complete resection; survival times are prolonged and extend to several years (Trout 1997, Trout et al 1995). Complete resection is recommended as neoplastic changes have been seen in some feline adenomas.

Myelolipomas present as single or multifocal masses of well-differentiated adipose tissue with normal haematopoietic elements. They have an excellent prognosis when treated with liver lobectomy (McCaw et al 1990).

Hepatocellular tumours

Hepatocellular carcinomas (HCC)

HCC is the most common primary hepatobiliary tumour in dogs (>50%), with a reported metastatic rate ranging from 22 to 61% (Patnaik et al 1980, 1981b, Trigo et al 1982). The massive form is most common, and usually affects a single lobe (**Figure 16.1**). Left lobes are more often affected (Patnaik et al 1980). Distant metastatic rate is high, depending on type: 100% for diffuse form, 93% for nodular form and 36% for massive type (Patnaik et al 1980). HCCs usually metastasize to regional lymph node, lung and peritoneum.

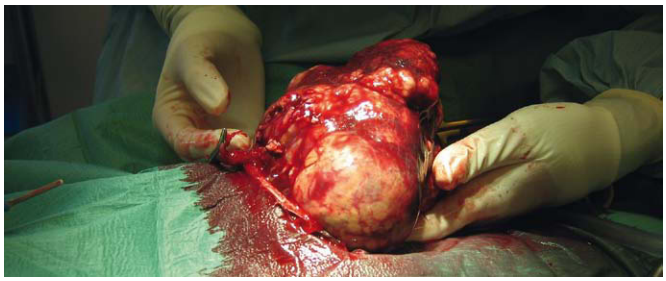

Figure 16.1 Massive hepatocellular carcinoma in a dog.

Low-grade HCC has a good prognosis with lobectomy. Surgery in 18 dogs with HCC showed 50% alive at 377 days without evidence of local recurrence or metastasis and the majority dying of unrelated causes (Kosovsky et al 1989). Most massive HCCs in dogs are resectable with partial or complete liver lobectomy, and have an excellent prognosis (MST of >1460 days, with no local recurrence and a metastatic rate of 5%). For massive HCC treated conservatively, the MST was 270 days and dogs treated conservatively were 15 times more likely to die of HCC (Liptak et al 2004).

Hepatocellular adenoma

Benign tumours are more common than carcinomas. They are usually incidental but have been reported to cause clinical signs of vomiting, diarrhoea, lethargy and inappetence (Eves 2004). Usually they are single masses but may be multiple and pedunculated.

Hepatoblastoma

There is only one reported case (Shiga et al 1997) of hepatoblastoma in a dog.

Bile duct tumours

Biliary carcinoma

Biliary carcinoma comprises 22–41% of malignant hepatobiliary tumours (second most common) (Patnaik et al 1980, Trigo et al 1982). Intrahepatic biliary carcinoma is more common than extrahepatic (**Figure 16.2**). These tumours can be solid or cystic (cystadenocarcinoma) (Patnaik et al 1981a). They can be massive, nodular or diffuse, and are highly metastatic (56–88%) (Patnaik et al 1981a, Strafuss 1976, Trigo et al 1982).

Prognosis with surgery is guarded (Fry & Rest 1993).

Biliary adenoma

Biliary adenoma is uncommon.

Gall bladder tumours

Gall bladder tumours account for <5% of biliary carcinomas in dogs and cats (Hayes et al 1983, Patnaik 1992, Patnaik et al 1981a).

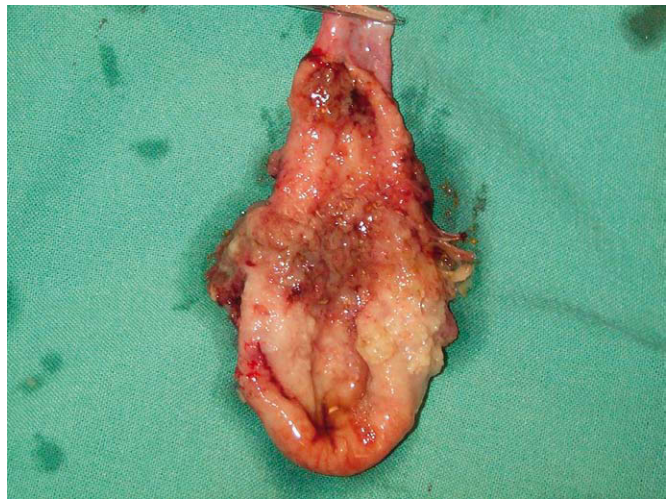

Figure 16.2 Biliary carcinoma in a dog – open gall bladder. (Courtesy R Straw.)

Neuroendocrine tumours

A hepatic carcinoid is an APUDoma. These arise from neuroectodermal tissue of the amine precursor uptake and decarboxylation cells (APUD) of biliary epithelium. They may secrete vasoactive peptides and amines. Hepatic carcinoids comprise a small percentage of primary intrahepatic tumours in dogs and cats (also primary gall bladder in one dog) (Willard et al 1988). They are known to behave very aggressively, with diffuse liver involvement and early metastasis (metastatic rate 93%), most commonly to the peritoneal wall and adjoining lymph nodes (Patnaik et al 1981c).

Sarcomas

Sarcomas comprise a small percentage of hepatic tumours. Most are locally aggressive and diffuse with early metastasis (metastatic rate 86%), commonly to spleen (Patnaik et al 1980). Leiomyosarcoma is the most common, then haemangiosarcoma, haemangioma, fibrosarcoma, osteosarcoma, chondrosarcoma, malignant mesenchymoma, botryoid rhabdomyosarcoma and liposarcoma.

History and clinical signs

More than 50% of cats have no clinical signs (most of these tumours were benign) (Lawrence et al 1994). When clinical signs do occur in dogs and cats, they are generally vague, nonspecific signs such as anorexia, weight loss, vomiting, lethargy, pyrexia, polyuria/polydipsia (PU/PD), abdominal distension and hepatomegaly. Between 50 and 75% of dogs and cats have a palpable cranial abdominal mass (Kosovsky et al 1989, Lawrence et al 1994, Post & Patnaik 1992, Trigo et al 1982). Icterus is usually not a feature. Hepatoencephalopathy can be seen if advanced.

Diagnostic work-up

Serum biochemistry changes include increased liver enzymes (Liptak 2007). Alkaline phosphatase (ALKP) may be increased

secondary to cholestasis, and ALT and AST increased because of hepatocellular necrosis or production from neoplastic tissues. Increased fasting and postprandial bile acids are seen in 50–75% of cases (non-specific) (Center et al 1985, 1986, 1991). Hypoglycaemia is seen in up to 38% of dogs with hepatobiliary tumours (Strombeck & Qualls 1978). Hypoalbuminaemia may result in ascites. Cats are often azotaemic, and those with malignant liver masses tended to have higher ALT, AST and total bilirubin (Lawrence et al 1994, Patnaik 1992, Post & Patnaik 1992).

Haematological changes include non-regenerative anaemia (common) and leucocytosis as non-specific findings (Kosovsky et al 1989, Patnaik et al 1980). Decreased clotting factors may cause coagulopathies, but clinical problems with coagulation are uncommon except for hepatic haemangiosarcoma (Thamm 2001). Platelet count is also important; thrombocytosis is seen in about 50% of dogs with the massive form of HCC (Liptak et al 2004).

Staging

Radiography

Thoracic radiographs rarely show metastatic disease at diagnosis (Evans 1987).

Ultrasound

Abdominal ultrasound is important for staging and biopsy. Ultrasound-guided biopsies may be obtained if the clotting profile is normal. Ultrasound appearance does not correlate well to histological type but focal masses are more likely to be HCC.

Ultrasound-guided fine needle aspirate (FNA) may be beneficial as a preliminary screen. There is overall agreement between histopathological diagnosis and cytological diagnosis in about 30% of canine and 50% of feline cases (Wang et al 2004). Ultrasound-guided tru-cut biopsy of various abdominal structures (not just liver) gave a correct diagnosis in 93.5% of cases with 5.6% minor complications and 1.6% major complications (Léveillé et al 1993).

In another study, only 65% of core hepatic biopsies provided a definitive diagnosis (Barr 1995). Another paper showed that wedge biopsies correlated to core biopsies (obtained at surgery from the same liver lobe in the same dog or cat) only about 50% of the time (Cole et al 2002). Core biopsies of the liver should therefore be interpreted with caution.

CT/MRI/laparoscopy

Laparoscopy would allow direct visualization of liver tissue, and likely an improved ability to obtain diagnostic liver biopsies compared to ultrasound. CT and MRI image more of the hepatic parenchyma and extrahepatic structures than ultrasound can allow, particularly when a large liver mass (or masses) obscure adjacent structures. However, imaging alone will not provide a definitive diagnosis.

Surgery

Exploratory surgery and biopsy may be necessary for staging, prognosis and definitive treatment.

Treatment

Surgical excision is the treatment of choice. Up to 80% of the liver can be resected, with hepatic regeneration complete in 6–8 weeks. In the authors' opinion, surgical stapling equipment (TA 30, 55 or 90) is preferred for liver lobectomy as it provides excellent haemostasis, is safe, reliable, easy to use and fast, and the margin of normal tissue is maximized (compared to finger dissection and suturing). These benefits compensate for the increased cost compared to sutures.

Suture fractionation/guillotine method can be used for removal of smaller liver masses or liver biopsy.

Liver biopsy can also be performed using haemostats placed on the edge of the liver lobe, and a scalpel blade used to cut liver on the other side of the haemostat. The haemostat should be left on for 5 minutes. Punch biopsy instruments (usually used for cutaneous lesions) may also be used to obtain liver biopsies.

Hypoglycaemia may occur after removal of 70% of the liver. Glucose returns to 70% of preoperative value within 6 hours, but close monitoring of blood glucose and supplementation with a glucose drip of up to 1 g glucose/kg/hr (10% solution) may be required intra- and postoperatively.

The presence of satellite lesions with a solitary hepatic lesion is not a contraindication to surgery. However, satellite lesions should be biopsied for confirmation. Surgery may be palliative to remove bleeding masses, even with metastatic disease.

Liver tumours are poorly responsive to systemic chemotherapy, and radiation is rarely applicable in their management.

New approaches to the treatment of non-resectable liver tumours include interventional radiography to deliver cytotoxic agents directly to the tumour.

Prognosis

For benign tumours and low-grade carcinomas treated with partial hepatectomy, the prognosis is good. Diffuse neoplasia has a poor prognosis. The role of systemic chemotherapy in the management of hepatic tumours has not been proven.

Tumours of the exocrine pancreas

Pancreatic adenocarcinoma is a cancer of the exocrine pancreas, originating in either acinar cells or ductular epithelium. It is rare in dogs and very rare in cats. Female dogs appear predisposed, as do Airedale Terriers, Boxers and Cocker Spaniels (Neiger 2003b), but any breed can be affected. Older dogs and cats (mean age 10–12 years) are most commonly affected.

Metastasis to regional and distant sites is frequent and often occurs prior to diagnosis (78%). Metastatic sites include liver, duodenum, mesenteric lymph node and mesentery resulting in carcinomatosis.

Clinical signs

Generally non-specific signs such as vomiting, anorexia, weakness, weight loss, abdominal pain, palpable abdominal mass, maldigestion, exocrine pancreatic insufficiency, icterus with obstruction of the common bile duct, abdominal effusion secondary to carcinomatosis, and paraneoplastic alopecia have been reported in cats (Brooks et al 1994, Tasker et al 1999).

Diagnostic work-up

Blood tests may show non-specific changes such as anaemia, neutrophilia and bilirubinaemia. Increases in serum amylase and lipase are inconsistent (Quigley et al 2001).

Barium studies may reveal slow intestinal transit time or invasion or compression of the duodenum. A pancreatic mass is detected with either radiography or ultrasonography in 50% of cases. In a series of 14 cats with malignant pancreatic tumours, the most common radiographic finding was an abdominal mass or mass effect (6/6) and a lack of serosal detail (4/6).

Ultrasound has been the imaging tool of choice as pancreatic carcinomas are frequently identified. Evaluation of regional lymph nodes is also achieved at the same time. There was a tendency for neoplastic lesions to manifest as single large lesions and for nodular hyperplasia to manifest as multiple smaller lesions (Hecht et al 2007). Ultrasound-guided FNAs when possible may be beneficial to differentiate carcinoma from other differentials, as in one study a correct diagnosis of pancreatic adenocarcinoma in 92% of patients was obtained (Bennett et al 2001). Cytology of ascitic fluid may also yield a diagnosis. Advanced imaging with contrast-enhanced CT is likely to be of increasing value in defining pancreatic tumours.

Differential diagnosis

Other pancreatic neoplasias (lymphoma, squamous cell carcinoma and lymphangiosarcoma) are reported (Hecht et al 2007), as well as pancreatic nodular hyperplasia (common incidental finding), pancreatic pseudocyst, adenoma, abscess and pancreatitis.

Treatment

Generally surgery is only done to obtain a diagnosis. Surgery to remove the pancreas involves significant morbidity and is highly unlikely to increase survival, especially in the presence of metastasis. Other therapies such as chemotherapy and radiation are unrewarding. Anecdoctal reports of responses with imatinib mesylate (Gleevec), a tyrosinase inhibitor, may indicate that a chemotherapeutic option may be available, if further studies confirm this.

Prognosis

Prognosis is poor, due to location, invasiveness and metastasis, with 12-month survival rate not reported (Seaman 2004).

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Tumours of the urogenital tract

TUMOURS OF THE FEMALE GENITAL TRACT

Canine mammary tumours

Mammary tumours are the second most common tumours of dogs (second to skin tumours) (Moulton 1999) (**Figure 17.1**). Mammary tumours are still frequently encountered in countries were ovariohysterectomy (OHE) or ovariectomy is not routinely performed on young female dogs that are not acquired for breeding purposes. A number of studies have shown that early OHE protects female dogs from developing mammary cancer in later life. The risk of developing mammary cancer if spayed prior to first heat is 0.05%, 8% after 1st, and 26% after 2nd, compared to intact dogs (Schneider et al 1969). OHE after four or more cycles or greater than 2.5 years of age has little or no protective effect on the development of malignant mammary tumours (Misdorp 1988, Schneider et al 1969). It is therefore a preventable condition and as such client counselling and veterinary surgeon awareness will continue to reduce the incidence of this preventable cancer.

Pathogenesis

The correlation with protection against developing mammary tumours and OHE indicates priming of the mammary tissue under hormonal influence. Prolonged, dose-related exposure to synthetic progestins has been shown to induce proliferation of mammary epithelial cells, potentially leading to genetic errors that may subsequently result in the development of mammary tumours (benign and malignant) (Misdorp 1991, Støvring & Glattre 1997). Administration of diethylstilboestrol is associated with ovarian tumour development but not mammary (Jabara 1962a,b).

The exact mechanisms and interactions at the cellular level that lead to the development of malignant mammary tumours are unknown. Hormonal therapy (anti-oestrogen drugs such as tamoxifen) has been shown to delay the onset of metastatic disease in humans with oestrogen receptor-positive tumours. The presence of oestrogen, progesterone and prolactin receptors on canine mammary tissue and tumours has been evaluated (Rutteman & Misdorp 1993). Only 50% of malignant primary tumours were positive for these receptors and they were infrequently detected on metastatic lesions.

The role of dietary factors in the development of canine mammary tumours is undetermined although one study did indicate that obesity at 1 year of age may lead to an increased risk of developing mammary neoplasia (without consideration of OHE) (Pérez-Alenza et al 1998).

Clinical signs

The presence of a mass associated with the mammary tissue warrants investigation. The caudal mammary glands are said to be more frequently involved than the cranial glands, and tumours can present as either isolated lumps or multiples. In the case of multiple lumps, each one must be treated as an individual. Usually, these lumps are non-painful; they may appear and remain static or grow rapidly. Cystic lesions can also be present in the mammary tissue, but care is required when evaluating such lesions as there may be underlying tumour associated with what appears cytologically to be cystic fluid.

Evaluation of the patient

Signalment

Most mammary tumours arise in middle-aged intact females with a peak incidence between 6 and 10 years of age (Egenvall et al 2005). Mammary cancer in males is rare (<1% of all mammary tumours occur in males) (Lana et al 2007), and female dogs are 62 times more likely to develop mammary gland tumours than male dogs (Saba et al 2007). In a recent study of eight male dogs with mammary tumours, seven out of eight tumours were benign, for which surgery alone provided long-term control (Saba et al 2007). Affected male dogs may have an oestrogen-secreting Sertoli cell tumour of the testis (Moulton 1999).

Mammary neoplasia is rarely seen in young dogs (Egenvall et al 2005); however, benign cystic hyperplasia can be seen in dogs involving all mammary glands. This is typically seen in dogs during metoestrus, pregnancy or after treatment with progestins. This usually resolves without surgical intervention (Rutteman & Kirpensteijn 2003).

History

It is important to ascertain the reproductive status of the patient, the stage of oestrus cycle, the time the lump has been present and if it has grown since first noticed.

Physical examination

A good physical examination is required. The mammary lump should be palpated for size, whether fixed to underlying tissue or freely movable, any enlargement of the draining lymph nodes, and any ulceration or oedema. These findings, coupled with the client's perception of rate of growth, are all indicators of potential malignancy.

Cytology

Fine needle aspiration (FNA) cytology to differentiate benign mammary adenoma from malignant carcinoma is generally

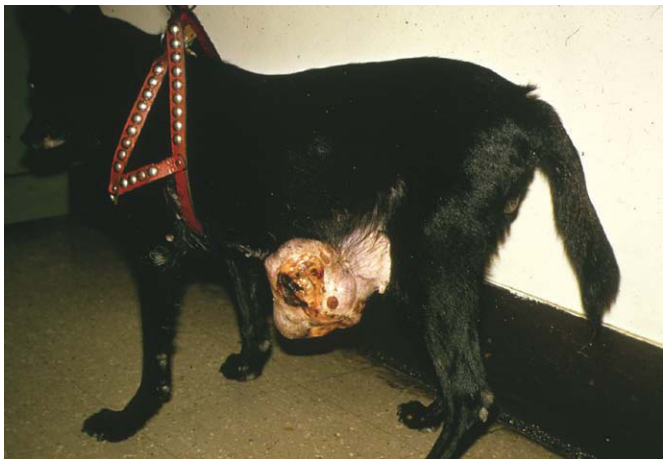

Figure 17.1 Large mammary gland tumour in a dog. (Courtesy S Withrow.)

unhelpful, due to mixed cell populations within mammary tumours.

Biopsy

Incisional biopsies give more information than cytology and may be useful to assist in staging and surgical planning; however, excisional biopsies are often more appropriate to provide diagnosis, prognosis and treatment in one step (see surgical treatment below). If an incisional biopsy is taken it is still important to submit the final specimen for evaluation by a pathologist; more than one benign biopsy has been shown to have a malignant component on final histopathology.

Staging the patient

Approximately 50% of mammary tumours are benign adenomas that are curable with adequate surgery (Brodey et al 1983, Gilbertson et al 1983). A large percentage of mammary carcinomas are low grade and carry a fair prognosis with adequate excision. The prognosis for non-invasive carcinoma is very good (Kurzman & Gilbertson 1986). Aggressive carcinomas are seen less frequently but warrant a guarded prognosis (Kurzman & Gilbertson 1986). Inflammatory carcinomas warrant a very poor prognosis, with a median survival time (MST) of 25 days with palliative care (Peña et al 2003, Pérez-Alenza et al 2001).

For a patient with suspected malignant mammary cancer, staging is important. The tumour/node/metastasis (TNM) system proposed by the World Health Organization (WHO) is typically used to stage veterinary patients with mammary tumours (Table 17.1).

1. Establish a minimum database of routine biochemistry, haematology and urinalysis.
2. Physically check the draining lymph nodes for any enlargement. If palpable, FNA of the regional lymph node should be taken and evaluated for neoplastic cells.
3. Thoracic radiographs, good quality right and left laterals are required to assess for metastatic disease. CT may be of more use for the detection of pulmonary metastatic disease from mammary gland neoplasia, as radiographs are not very sensitive, detecting metastasis in only one of six dogs with necropsy-confirmed intrathoracic metastasis (Baumann et al 2004). Furthermore, CT has been shown to be more sensitive than radiographs for detecting pulmonary metastases (Nemanic et al 2006). Clinical and histological staging of mammary tumours are shown in Table 17.2a,b.

Table 17.1 WHO staging of canine mammary tumours

Tumour	Regional lymph node (LN)	Distant metastasis
T0: no measurable tumour	N0: no LN metastasis	M0: no distant metastasis
T1: <3 cm	N1: LN metastasis	M1: distant metastasis
T2: 3–5 cm		
T3: >5 cm		
T4: inflammatory Ca		
a: not fixed	a: not fixed	
b: fixed	b: fixed	

(With permission from the World Health Organization.)

Table 17.2a Clinical staging of canine mammary tumours

Clinical stage	Tumour	Regional lymph node	Metastasis
I	T1	N0	M0
II	T0, T1	N1	M0
	T2	N0, N1	M0
III	T3	N0, N1	M0
	T0–T3	N1	M0
IV	T0–T3	N0, N1	M1
V	T4	N0, N1	M1

After Owen (1980).
(With permission from the World Health Organization.)

Table 17.2b Histological staging of canine mammary tumours

Stage	
0	Tumour cells limited to ductal tissue
I	Tumour cells invading stromal tissue
II	Vascular/lymphatic invasion, regional lymph node metastasis
III	Distal metastasis present

After Gilbertson et al (1983).

Poor prognostic signs

- Inflammatory (Peña et al 2003, Pérez-Alenza et al 2001)
- Size (<3 cm better than >3 cm) (Bostock 1986, Chang et al 2005, Kurzman & Gilbertson 1986, Philibert et al 2003)
- Ulceration (Chang et al 2005, Hellmén et al 1993, Pérez-Alenza et al 1997)
- Node positive (for stage, see Table 17.2b) (Chang et al 2005, Gilbertson et al 1983, Hellmén et al 1993,

Karayannopoulou et al 2005, Kurzman & Gilbertson 1986, Yamagami et al 1996)
- Histological type and grade (Benjamin et al 1999, Chang et al 2005, Gilbertson et al 1983, Hellmén et al 1993, Karayannopoulou et al 2005, Kurzman & Gilbertson 1986, Misdorp et al 1971, Peña et al 2003, Pérez-Alenza et al 2001)
- Invasiveness (including fixation to underlying tissue) (Gilbertson et al 1983, Hellmén et al 1993, Kurzman & Gilbertson 1986)
- Presence of distant metastasis (Chang et al 2005)
- Degree of nuclear differentiation (Gilbertson et al 1983, Karayannopoulou et al 2005)
- Evidence of lymphoid cellular reactivity in tumour vicinity (Gilbertson et al 1983)
- Intravascular growth, steroid hormone receptor activity (Geraldes et al 2000, Nieto et al 2000)
- S-phase fraction (Hellmén et al 1993)
- High Ki-67 proliferation indices (Zuccari et al 2004)
- DNA aneuploidy (Hellmén et al 1993)
- Number of argyrophilic nuclear organizer regions (AgNORs) (Bostock et al 1992)
- Higher angiogenesis (Restucci et al 2000)
- Tumours present for >6 months had a higher risk of lymph node metastasis (Chang et al 2005).

Non-prognostic signs

- Gland involved (Schneider et al 1969)
- Type of surgery (MacEwen et al 1985)
- Spaying at time of treatment (some controversy but needs more study) (Chang et al 2005, Morris et al 1998, Sorenmo et al 2000, Yamagami et al 1996)
- Multiple lumps (Benjamin et al 1999, Moulton et al 1986).

Malignant mammary tumours

Whilst approximately 50% of canine mammary tumours are benign, between 20 and 40% are considered to be malignant and can arise from different structures within the mammary tissue (Brodey et al 1983, Gilbertson et al 1983).

Carcinomas

Mammary carcinoma (adenocarcinoma) is the most common malignant tumour and is variously described as solid, tubular or papillary. They can be simple (epithelium alone) or complex (epithelium and myoepithelium). The infiltrative characteristics of the tumour in conjunction with the degree of invasion into local lymphatics and capillaries are important in determining the long-term prognosis regarding local recurrence and metastatic potential. The most aggressive carcinomas have lost their identifying characteristics and are described as anaplastic or poorly differentiated tumours; the latter warrant a guarded prognosis.

Histological grade 0 has a 19% recurrence compared to 97% for grade II (Gilbertson et al 1983). Also similar with nuclear differentiation, poorly differentiated had 90% recurrence, 68% with moderate and 24% with well differentiated (Gilbertson et al 1983). The most common metastatic sites for mammary carcinomas are the draining lymph nodes, followed by the lungs. Bone, liver or brain metastases are less frequent in veterinary patients compared to human patients (Lana et al 2007).

Inflammatory carcinomas

- Severe and rapid spread
- Red, hot, painful, pruritic
- Spreads laterally down legs and across midline
- Inoperable

Inflammatory carcinomas are rare neoplasms with an extremely poor prognosis. These tumours can often be identified at the time of presentation. Typically, physical examination reveals a firmly attached mass that is painful, erythematous and warm. It may extend to involve multiple glands and cause oedema of the peripheral limb (**Figure 17.2**). These patients are typically in chronic disseminated intravascular coagulation (DIC).

Typically thoracic radiographs are unremarkable on presentation, but in the few patients that survive greater than 60 days pulmonary metastases will become apparent. In those cases where surgical intervention has been attempted, the complication rate was high due to the rapid recurrence and regional spread of tumour. Histology on these tumours shows significant infiltration of neoplastic cells into the lymphatics, explaining the clinical presentation of oedema.

Anecdotally, radiotherapy as a palliative procedure may improve quality of life for a short period of time in certain patients but the overall prognosis for any patient with inflammatory mammary carcinoma is poor (Peña et al 2003, Pérez-Alenza et al 2001).

Malignant mixed tumours

These arise from both the epithelial and connective tissue components of the mammary gland. They are also known as 'carcinosarcomas' and are relatively uncommon.

Other mammary tumours

- *Sarcomas*: These are rare tumours of the mammary gland and the origin within the mammary tissue is unknown. Sarcomas are considered to have poor prognosis. Most dogs die within 9–12 months (Hellmén et al 1993, Misdorp et al 1971).

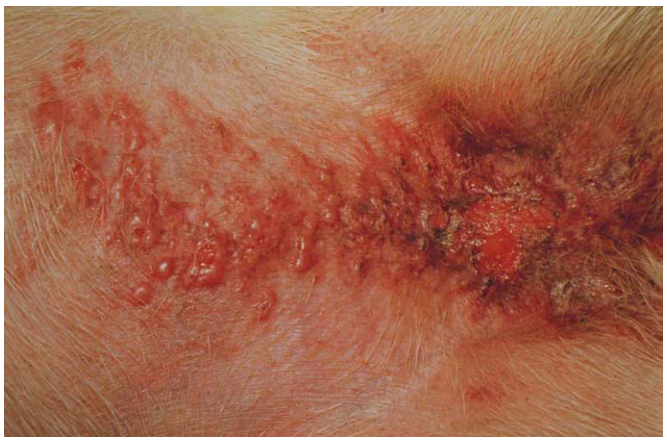

Figure 17.2 Inflammatory carcinoma. (Reproduced from Small Animal Clinical Oncology 3rd edition, S Withrow & E G MacEwan, 2001, with permission from Elsevier.)

- *Extraskeletal osteosarcoma*: These are also rare tumours and warrant a guarded prognosis due to early metastatic spread, primarily to the lungs (Kuntz et al 1998, Langenbach et al 1998)
- *Mast cell tumours*: These should be managed as with any mast cell tumour (see Chapter 19).
- *Lymphoma*: Lymphoma has been reported as an isolated mass in the mammary tissue as a rare occurrence.

Treatment

Surgery

Important features are size and invasiveness or adherence. The treatment of choice is surgical excision with appropriate margins. No clinical trial has shown improvement in survival with radical versus local removal.

OHE when mammary tumours are removed does not have a significant effect on the progression of malignant disease (Morris et al 1998, Yamagami et al 1996). In another study, however, OHE at the time of mammary tumour removal improved survival 2 years after surgery, and was more beneficial for complex carcinomas than for simple carcinomas (Chang et al 2005). Sorenmo et al (2000) also found a beneficial effect of OHE at the time of mammary tumour removal. One-quarter of dogs with benign mammary tumours developed another mammary tumour within 2 years, whether they were spayed or not (Morris et al 1998). OHE helps prevent the development of further benign mammary tumours.

Goal of surgery

Remove the entire tumour by the simplest procedure (**Figure 17.3**). More surgery is not better surgery.

Surgical procedures

- *Lumpectomy*: Lumpectomy is performed for small nodules <0.5 cm that are firm and superficial. Incomplete margins are acceptable for benign lesions but if malignant, re-excision to achieve clean margins is warranted.
- *Mammectomy*: Mammectomy to remove the whole gland is used for centrally located tumours, >1 cm, or with any degree of fixation to skin. Skin and abdominal wall fascia should be removed if involved. For malignant lesions, margins of 1–2 cm of grossly normal tissue are generally adequate.
- *Regional mastectomy*: As above, with several glands removed together for ease of surgery (e.g. glands 1, 2 and 3 together or glands 4 and 5 together). The inguinal lymph node is usually removed en bloc with glands 4 and 5. The axillary lymph node is only removed if enlarged or cytologically positive for metastasis.
- *Unilateral (1–5) mastectomy*: Performed to achieve multiple lumpectomies with greater ease and rapidity. It does not improve survival compared with multiple lumpectomies or mammectomies (MacEwen et al 1985). In dogs, there is minimal need for a bilateral (radical) mastectomy. There is usually also minimal loose skin to allow this to be achieved with clean margins. A better approach would be to do staged unilateral mastectomies, ensuring adequate margins are achieved with each surgery. As 50% of canine mammary tumours are benign, it is important to *not* perform a 'malignant' surgery for a benign disease. More surgery, if required, can be done later.
- *Bilateral (radical) mastectomy*: This entails considerable morbidity, time and money and does not change survival, compared to multiple mammectomies/lumpectomies.

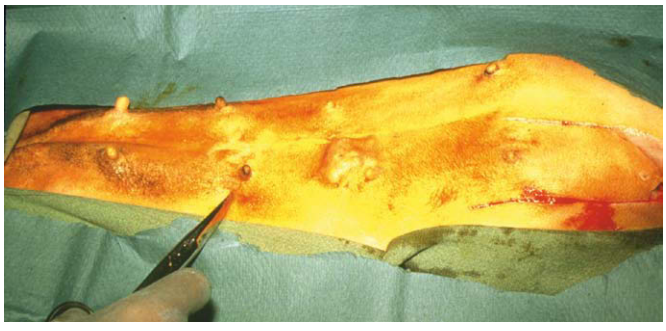

Figure 17.3 Intraoperative mastectomy. (Courtesy S Withrow.)

Other treatments

Chemotherapy

For patients with aggressive mammary tumours exhibiting lymphatic or vascular invasion there is a high rate of local recurrence and metastasis. However, the role of adjuvant chemotherapy in these patients has not been adequately determined. Single-agent doxorubicin (Hahn et al 1992), doxorubicin and cyclophosphamide, and doxorubicin and docetaxel (Simon et al 2006) are chemotherapy protocols that have been used for veterinary patients with aggressive mammary carcinomas. Anecdotally, some patients are reported to have benefited from doxorubicin-based chemotherapy but prospective studies are few in number and have shown equivocal benefit from adjuvant chemotherapy. Local recurrence can be re-addressed by surgery and a second surgical procedure should be considered if the margins are not adequate. Chemotherapy should be reserved for patients at risk from metastases.

Radiotherapy

Radiotherapy is rarely used in the management of canine mammary cancer, but undoubtedly has a role for patients with locally recurrent disease that is not amenable to further surgery or for patients with regional metastasis to lymph nodes also not amenable to surgery. In such cases, radiation would be considered a palliative treatment.

Hormonal therapy

For patients diagnosed with mammary carcinoma, no benefit has been shown to carrying out OHE at the time of mastectomy (Morris et al 1998). This was to be expected due to the low levels of receptors identified on mammary tumours. In human patients anti-oestrogen drugs such as tamoxifen are effective in delaying the development of metastatic disease in those patients with oestrogen-positive tumours. No such benefit has been noted in canine patients and the oestrogenic effect of tamoxifen on the uterus resulting in pyometra or stump pyometra is an undesirable side effect. However, this drug may benefit the small number of dogs that have tumours that are oestrogen receptor positive but to establish the benefit a prospective trial would be required on suitable candidates (Morris et al 1993). At the present time there is little

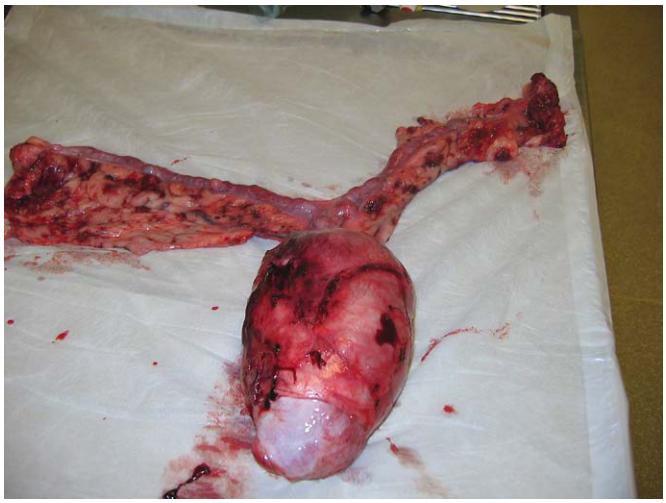

Figure 17.4 Uterine leiomyoma.

indication that hormonal therapy is of benefit to canine patients.

Tumours of the uterus

Neoplasia of the uterus is uncommon in dogs, primarily because of the large percentage of dogs that undergo elective OHE. Most uterine tumours encountered in dogs are of mesenchymal origin (85–90% benign leiomyomas, 10% leiomyosarcomas) (Theilen & Madewell 1979). Other malignant tumours of the canine uterus sporadically reported include carcinoma (Cave et al 2002, Murakami et al 2001, Payne-Johnson et al 1986, Pena et al 2006, Vos 1988).

Clinical signs

Clinical signs are non-specific and these tumours may be an incidental finding. In some cases a mass can be palpated, or a vaginal discharge may be present.

Imaging

Abdominal radiographs may show the presence of a soft tissue mass consistent with the uterus. Abdominal ultrasound is useful as this allows better delineation of tumour and assessment of the regional lymph nodes for evidence of metastasis.

Treatment and prognosis

The treatment of choice is OHE (**Figure 17.4**). The value of chemotherapy or radiotherapy is unknown.

In general, the prognosis for dogs with uterine tumours is good as the majority are benign.

Tumours of the vagina and vulva

Tumours of the vagina and vulva are seen with greater frequency than tumours of the ovary or uterus. Most of these tumours are of mesenchymal origin (Table 17.3).

Leiomyomas are typically seen in older (10–11-year-old) intact females and account for approximately 85% of all vaginal and vulval tumours in dogs (Kydd & Burnie 1986, Thacher & Bradley 1983). Production of oestrogen is associated with growth of these tumours. The malignant variant, leiomyosarcoma, is the most common malignant tumour of the vagina and vulva. Leiomyosarcomas are locally invasive but are slow to metastasize.

Other tumours reported in this region are rhabdomyosarcomas, mast cell tumours, haemangiosarcoma, squamous cell carcinoma (SCC), adenocarcinoma, epidermoid carcinoma, osteosarcoma and transmissible venereal tumours (Brodey & Roszel 1967, Herron 1983, Hill et al 2000, Suzuki et al 2006, Thacher & Bradley 1983, Theilen & Madewell 1979).

Table 17.3 Tumours of the vagina and vulva

Benign	Malignant
• Leiomyoma • Fibroma • Fibroleiomyoma • Lipoma	• Leiomyosarcoma • Adenocarcinoma • Fibrosarcoma • Transmissible venereal tumour (TVT)

Clinical signs

These are usually associated with the size and position of the mass as these tumours can be either extra- or intraluminal growths. Patients can present with a bulging of the perineum, prolapse of tumour from the vulva, dysuria, stranguria, haematuria, vulval bleeding or discharge, or tenesmus.

Physical examination

An obvious swelling or protruding mass from the vulva may be visible on examination of the perineum and confirmation of location of the mass can be obtained via digital examination per rectum or per vagina.

Diagnostic work-up

Routine blood work is usually unremarkable; however, anaemia, hypoproteinaemia and thrombocytopenia may occur due to chronic blood loss, and hypoglycaemia is a possible paraneoplastic syndrome. Secondary infections may also occur, causing a leucocytosis.

Imaging

Radiographs and ultrasound have limited application due to the intrapelvic location of these tumours. Contrast radiographic studies including positive contrast retrograde vaginourethrography are useful to determine the size and extent of the primary. Chest radiographs are indicated to rule out pulmonary metastases. Advanced imaging such as a CT scan may be beneficial.

Treatment

Surgical resection is complicated by the vascularity of the vagina and vulva, and the neovascularization that occurs with tumour growth. Blood loss during surgery can be considerable. The surgeon must obtain a packed cell volume (PCV) and total protein prior to surgery, monitor for intraoperative blood loss and have an ability to provide a blood transfusion if needed.

Vaginal leiomyomas and leiomyosarcomas are approached surgically via the perineum. If there is any evidence of a haem-

orrhagic or purulent vaginal discharge, or the tumour is palpable via the vagina (intraluminal), the tumour is expected to involve the inner layers of the vaginal wall and an episiotomy may be needed to facilitate exposure.

If the tumour is pedunculated and intraluminal, it may be removed after ligation with a transfixing suture. If it is more broad based it may be amenable to a debulking surgery or 'shelling- out', which is only appropriate for benign or histologically low-grade tumours.

If there is no vaginal discharge, and the tumour is palpated (by a combination of rectal and vaginal examination) to be arising from the outer vaginal wall (extraluminal), an episiotomy may allow adequate visualization; alternatively, a perineal approach to the dorsal, ventral or lateral vagina may be preferable.

If a preoperative incisional biopsy has shown a malignancy, e.g. an aggressive sarcoma, a squamous cell carcinoma or adenocarcinoma, a full thickness resection of the vaginal wall and tumour en bloc, followed by anastomosis of grossly normal vaginal wall (if possible) is required. The surgeon should ensure adequate exposure to confirm there is no iatrogenic damage to the urethra, and the urethra should be catheterized prior to surgery to aid intraoperative identification.

An incisional biopsy should always be performed prior to extensive surgical resections to allow the surgeon to best plan surgery to obtain a potential cure. A wider resection, such as vulvovaginectomy and perineal urethrostomy (Bilbrey et al 1989), may provide a cure or improved palliation for a malignant vaginal/vulval tumour, and attempts at surgical cure ought not to be thwarted by an extensive but 'dirty' surgery.

As leiomyomas, fibromas, polyps, leiomyosarcomas and most other vaginal tumours are hormone dependent, surgical excision of the vaginal tumour should be accompanied by OHE to prevent recurrence. The prognosis for adenocarcinoma and squamous cell carcinoma is poor due to metastasis or local recurrence, whereas benign or low-grade mesenchymal lesions have a good prognosis with treatment.

Tumours of the ovary

Ovarian tumours are rare in the dog, primarily because most dogs undergo OHE at a relatively young age and, when present, are typically seen in middle to older aged dogs.

Cystadenomas/carcinomas are the most common tumours encountered and account for approximately 50% of ovarian tumours (Nielsen et al 1976, Patnaik & Greenlee 1987). They can be either unilateral or bilateral. They arise from the surface epithelial layer of the ovary and malignant tumours metastasize to para-aortic lymph nodes, kidneys, omentum, liver and lungs. They will also seed tumour throughout the abdominal cavity, resulting in carcinomatosis and formation of a malignant effusion.

Granulosa cell tumour develops from the gonadostromal (sex cord) tissue of the ovary. These tumours are usually unilateral and about 20% are malignant with a similar metastatic pattern as seen with cystadenocarcinomas (Hayes & Harvey 1979, Herron 1983, Neilsen et al 1976, Patnaik & Greenlee 1987, Theilen & Madewell 1979). Granulosa cell tumours may be hormonally active and secrete oestrogen, and comprise 50% of ovarian tumours in some reports (Dow 1960, Herron 1983, Neilsen et al 1976, Patnaik & Greenlee 1987).

Other sex cord stromal tumours include the extremely rare and benign tumours thecoma and luteoma.

The third category of ovarian tumours includes the germ cell tumours – dysgerminoma and teratoma/teratocarcinoma. Dysgerminomas arise from undifferentiated germ cells and are considered to be malignant in that metastasis occurs to regional lymph nodes and other abdominal organs in approximately 10–30% of cases (Andrews et al 1974, Dehner et al 1970, Neilsen et al 1976). Teratomas are usually, but not always, benign and are often composed of two or three germinal layers including bone, cartilage, brain or glandular epithelium.

Clinical signs

Many tumours are incidental findings at the time of an elective OHE. However, an ovarian tumour should be suspected in any intact female with abnormal oestrus cycles. Signs consistent with excess oestrogen production may indicate the presence of a granulosa cell tumour.

Presenting signs may include prolonged oestrus, alopecia, mammary hyperplasia, cystic endometrial hyperplasia/pyometra, vaginal discharge, vulval swelling, attractiveness to males and very occasionally myelosuppression due to hyperoestrogenism. Other clinical signs that may be apparent include lethargy, abdominal distension, weight loss, presence of a palpable abdominal mass and lumbar pain.

Physical examination

Abdominal palpation may indicate the presence of an abdominal mass.

Diagnostic work-up

In patients with chronic hyperoestrogenism there may be evidence of bone marrow suppression on haematology. This is sometimes irreversible, even with removal of the primary tumour.

Imaging

Plain radiographs, including thoracic films, and ultrasonography will help define the presence and location of the mass and, especially with ultrasound, the possible presence of metastases.

Cytology

For patients with peritoneal effusion cytology is valuable to determine the presence of malignant cells.

Treatment

The treatment of choice for all patients that do not show extensive signs of metastasis is OHE. For those patients with benign tumours the prognosis is good. In patients with malignant tumours with evidence of regional spread the efficacy of chemotherapy has not been proven. Anecdotally, canine patients with carcinomatosis have responded to intracavitary cisplatin chemotherapy; however, as in humans, the effectiveness of treatment depends on overall tumour burden and patients with large intra-abdominal masses (>0.5 cm in diam-

eter) do not respond as well as patients with small nodules or neoplastic cells present in the effusion.

Ovarian carcinoma is rare in dogs, but as in humans the potential for local dissemination throughout the abdominal cavity is high.

Feline mammary tumours

Mammary tumours are the third most common neoplasm described in the cat after skin tumours and lymphoma/leukaemia (Carpenter et al 1987, Dorn et al 1968a,b, Hayes et al 1981). As with dogs, mammary tumours primarily affect female cats with an extremely low incidence in males. Also as with dogs, hormonal influences are believed to contribute to the development of mammary tumours as intact cats and cats treated with progestins have an increased risk of developing mammary tumours (approximately 10% risk of cancer with progesterone therapy). All glands are at equal risk (Anderson & Jarrett 1966, Hayden & Neilson 1971, Hayes 1977, Weijer & Hart 1983). Feline mammary tumours have been shown to express fewer steroid hormone receptors when compared to normal feline mammary tissue (Hamilton et al 1976, Hayden et al 1981).

Studies have shown that cats undergoing OHE prior to 1 year of age have a significantly reduced incidence of mammary carcinoma (Overley et al 2005). Early spaying is protective but not as absolute as in the dog. Parity has not been shown to be a risk factor in the development of feline mammary tumours (Misdorp 1991, Overley et al 2005).

Signalment

Most mammary tumours occur in middle-aged to older female cats, with a median age of 10–12 years. Siamese cats may be at higher risk of developing mammary tumours than other breeds and these are often bilateral (Kessler & von Bomhard 1997).

Clinical signs

Clinical signs are of a mass associated with the mammary gland that may be attached to underlying tissue or ulcerated. In some cases the tumour may be plaque-like in appearance. No other clinical signs may be apparent.

Diagnostic work-up

As these are usually older patients, routine biochemistry, haematology and urinalysis should be carried out.

Physical examination should include palpation of the regional lymph nodes. An aspirate of the nodule helps to rule out any other cause of a mammary-associated lump.

Chest radiographs are indicated (left and right lateral views) to rule out metastatic lesions. In cats with metastases the typical thoracic radiograph is that of an interstitial military pattern; pleural effusion can also be present (**Figure 17.5**). The presence of a malignant effusion warrants a poor prognosis.

Malignant mammary tumours

In the cat >85% of mammary tumours are malignant; the majority of these are carcinomas (Bostock 1986, Carpenter et al 1987, Hayes et al 1981) (**Figure 17.6**).

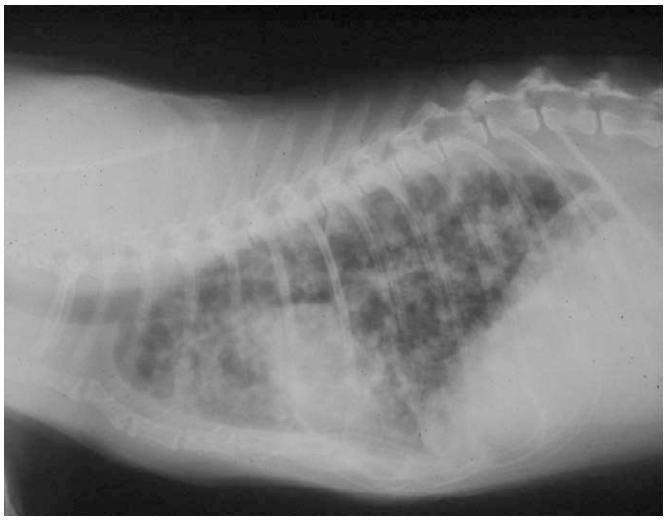

Figure 17.5 Pulmonary metastasis from feline mammary carcinoma. (Courtesy S Withrow.)

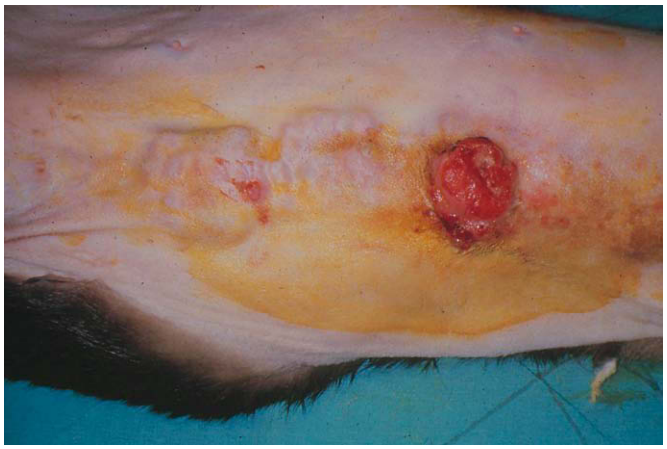

Figure 17.6 Ulcerated feline mammary carcinoma. (Courtesy S Withrow.)

Table 17.4 WHO staging system for feline mammary carcinomas

Stage	Tumour diameter
I	<1 cm
II	1–3 cm
III	>3 cm
IV	Distant metastases

(With permission from the World Health Organization.)

Staging

Because the majority of feline mammary tumours are malignant, staging is important and the WHO staging system for domestic animals recognizes four stages (Table 17.4). A number of studies have shown that the size of the primary at initial presentation is a good prognostic indicator and the staging system is based on tumour size (Hayes & Mooney 1985, MacEwen et al 1984, Weijer & Hart 1983).

The most significant factor affecting long-term survival in cats with mammary carcinoma is tumour size. For tumours

<2 cm, MST is >3 years, compared to 15–24 months for 2–3 cm lesions and 4–12 months for lesions >3 cm (Ito et al 1996, MacEwen et al 1984, Viste et al 2002).

Stage at the time of presentation is also prognostic, cats with stage I and early stage II disease having a longer MST (>3 years) than cats with stage II–III (MST >2 years) or late stage III–IV (MST 6 months) (MacEwen et al 1984). Extent of surgery is also prognostic, with local recurrence in two-thirds of cats with conservative resection (MacEwen et al 1984). Bilateral mastectomy resulted in an MST of 917 days, compared to 428 days for regional mastectomy and 348 days for unilateral mastectomy (Novosad et al 2006).

Treatment

Surgery

Radical surgery is indicated in the cat with mammary neoplasia. Unlike the dog, radical mastectomy has a better prognosis than lumpectomy, and more aggressive surgery improves overall survival (MacEwen et al 1984, Novosad et al 2006).

Radical (bilateral) mastectomy and bilateral inguinal lymphadenectomy are generally performed up front at the first surgery, as cats have more loose skin than dogs, and cats are therefore more amenable to this surgery (**Figure 17.7**). However, if preferred by the surgeon or the client, staged unilateral mastectomies may be performed (separated by 2 weeks), as this may be less traumatic for the cat. Bilateral (radical) mastectomies create a large wound, and care should be taken to avoid hypothermia. Pain management should also be accordingly aggressive, as should postoperative supportive care.

Mastectomy may be an appropriate palliative treatment, even in the cat with known metastasis, as ulcerated, bleeding, infected mammary cancers may cause significant morbidity, compared to pulmonary metastatic disease, which may be asymptomatic.

Chemotherapy

The role of adjuvant chemotherapy, either doxorubicin alone or doxorubicin in combination with cyclophosphamide, may have some benefit in prolonging survival in patients with late stage II to stage III disease, but large prospective studies have not been carried out to optimise chemotherapeutic protocols. The same combinations have been used in patients with inoperable disease where a 50% partial response rate was observed, and in those cats that did respond to chemotherapy the MST increased from 75 to 150 days.

The standard dose of doxorubicin was 1.0–1.1 mg/kg every 3 weeks for five treatments. The major side effect was mild anorexia at the lower dose; increasing the dose to 1.1 mg/kg is likely to result in more profound anorexia. Myelosuppression was generally not encountered (North & Mauldin 1997).

Radiotherapy

Radiotherapy is rarely used in the management of feline mammary tumours but may be of some benefit in those patients with inoperable tumours.

Feline mammary hypertrophic fibroadenoma complex (**Figure 17.8**)

This progesterone-dependent complex usually presents in young intact cats. It is induced in male and female neutered cats with exogenous progesterone.

Treatment is by OHE, usually via a flank approach to avoid the enlarged mammary glands.

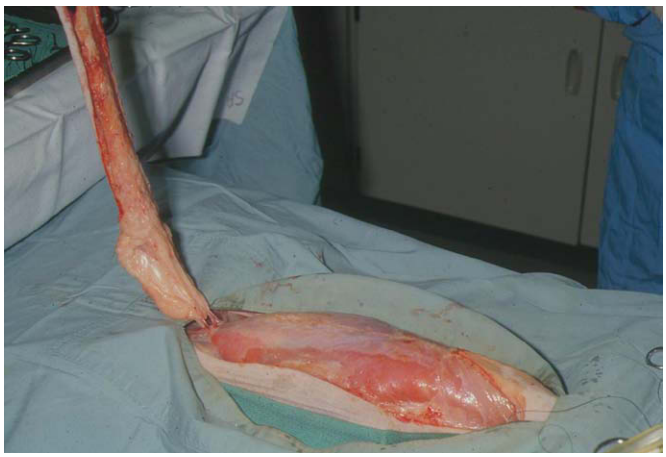

Figure 17.7 Bilateral mastectomy in a cat, intraoperative. (Courtesy S Withrow.)

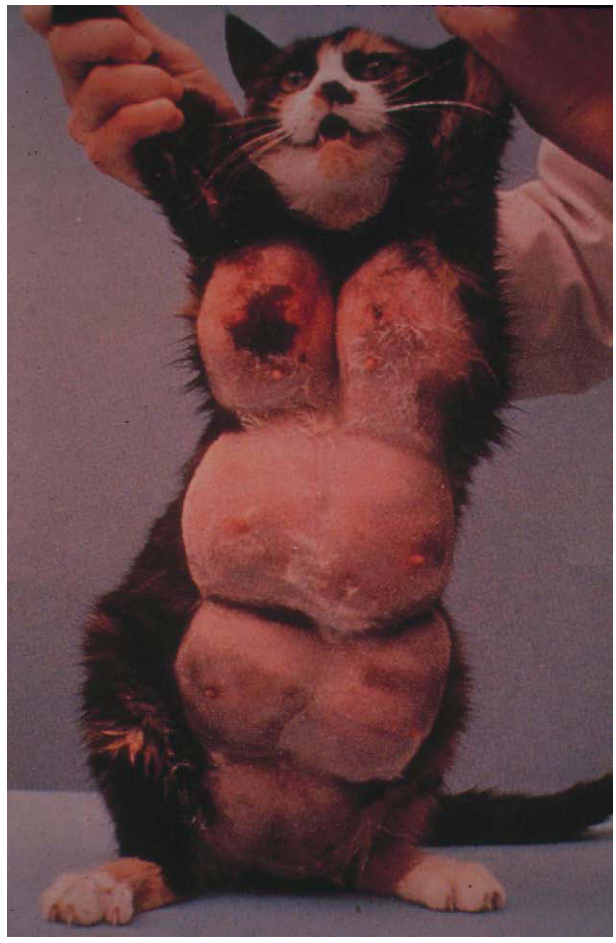

Figure 17.8 Feline hypertrophic adenoma complex. (Reproduced from Small Animal Clinical Oncology 4th edition, S Withrow & D Vail, 2007, with permission from Elsevier.)

Tumours of the ovary

Ovarian tumours are rare in the cat, accounting for only 3% of feline tumours. The reason for such a low incidence of ovarian cancer is probably related to the fact that most cats undergo OHE at a young age. The most common ovarian tumour seen in the cat is granulosa cell tumour, with clinical signs of paraneoplastic hyperoestrogenism common (Gelberg & McEntee 1985, Norris et al 1969).

Tumours of the uterus and cervix

Tumours of the uterus and cervix are uncommon in the cat. The most common malignant uterine tumour in the cat is adenocarcinoma (Miller et al 2003, O'Rourke & Geib 1970). Feline uterine sarcoma has also been reported (Cooper et al 2006, Miller et al 2003, Sato et al 2007).

Tumours of the vagina and vulva

These tumours are extremely rare in the cat; leiomyomas and fibromas have been reported.

TUMOURS OF THE MALE GENITAL TRACT

Tumours of the testicle

Tumours of the testicle are the most common tumours of the male genital tract, but as with mammary tumours in females are completely preventable by castration of male dogs not acquired for breeding purposes. One recent report found one or more testicular tumours in 27% of 232 necropsied dogs (Grieco et al 2008). Currently, these tumours account for 90% of all tumours of the male reproductive tract (Cotchin 1960, Hayes & Pendergrass 1976, von Bomhard et al 1978). They are typically seen in older male dogs, median age 10 years.

Cryptorchid dogs and dogs with inguinal hernias are at higher risk of developing testicular tumours and at an earlier age. Cryptorchid testes are 14 times more likely to develop neoplasia than scrotal testes, and dogs with inguinal hernias have a five times greater risk of testicular tumours (Hayes & Pendergrass 1976). About 50% of Sertoli cell tumours and about 30% of seminomas are in cryptorchids (Reif & Brodey 1969). The three most common testicular tumours are the Sertoli cell tumour, the interstitial cell tumour (Leydig) and the seminoma, each occurring with approximately equal frequency (Cotchin 1960). It is possible to get a combination of more than one type in one dog.

Clinical signs

The presence of an enlarged testicle or a mass within the testicle seen on routine examination is indicative of a testicular tumour. An abdominal mass may also be palpable, and testicular masses may be found on abdominal or testicular ultrasonography. Feminization syndrome may be the presenting clinical sign. An abdominal ultrasound is indicated to rule out a testicular tumour in any cryptorchid adult male dog.

Sertoli cell tumour (SCT)

Breed predisposition has been noted in Norwegian Elkhound, Fox Terrier, Afghan Hound, West Highland White Terrier, Airedale, Weimaraner, Pekingese and Shetland Sheepdog (Cooley & Waters 2001).

Clinical signs

About 50% of SCTs are found in cryptorchid testicles (Reif & Brodey 1969). SCTs can affect the ratio of oestrogen:testosterone (Mischke et al 2002). This ratio may be proportional to tumour size. The degree or presence of male feminization syndrome may depend on testicle location, with 16% of scrotal, 50% of inguinal and 70% of abdominal SCTs causing feminization syndrome (Lipowitz et al 1973). Oestrogen is bone marrow suppressive, and causes myelotoxicosis in 15% of SCTs with male feminization syndrome.

Clinical signs of male feminization syndrome include non-pruritic, symmetrical alopecia (beginning in the genital and perineal region and spreading to the ventral abdomen, thorax, flanks and neck), hyperpigmentation, gynaecomastia, galactorrhoea, penile atrophy and a pendulous prepuce, attractiveness to other males and standing in a female posture to urinate, symmetrical and squamous metaplasia of prostate, and atrophy of non-neoplastic testes.

Pathology

About 10–15% of SCTs are malignant (Fan & de Lorimier 2007), with metastasis to the inguinal, iliac and sub-lumbar lymph nodes as well as the lungs, liver, spleen, kidneys and pancreas. SCTs grow expansively to compress and destroy parenchyma.

Oestrogen myelotoxicosis often appears as an initial transient increase in granulopoiesis and a neutrophilic leucocytosis, followed by eventual hypoplasia of all cell lines and development of pancytopenia (thrombocytopenia, anaemia, granulocytopenia) (Sanpera et al 2002).

Diagnostic work-up and staging

This comprises abdominal and testicular palpation, rectal palpation, abdominal ultrasound, radiographs (abdominal and thoracic), exploratory abdominal surgery, haematology, increased plasma oestrogen, and histopathology following castration.

Treatment

Castration with a wide margin of spermatic cord is the treatment of choice. For the patient with bone marrow suppression, perioperative supportive care such as fluid therapy, blood transfusions, platelet-rich plasma and broad-spectrum bactericidal antibiotics is indicated. Corticosteroids, anabolic steroids and haematinics have unknown therapeutic benefits. Haematopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF) and erythropoietin may be tried.

Prognosis

Complete surgical resection is curative if there is no bone marrow hypoplasia or metastasis. Mortality rate is more than 70% with severe bone marrow depression (Sherding et al 1981). Haematological parameters can take months to normalize, despite removal of the source of oestrogen. However,

the prognosis for patients with myelotoxicity is always guarded, and persistent severe thrombocytopenia of more than 2 weeks' duration is a poor prognostic indicator. Dogs that survive have prolonged survival (sometimes more than 1 year) (Sherding et al 1981). Haemorrhage, depression, exercise intolerance and infections may occur with persistent pancytopenia.

Interstitial cell tumour

These are found in the fibrovascular stroma of the testicle. They are benign but functional. They are associated with prostatic disease and enlargement and perineal herniation (Cooley & Waters 2001). Breeds predisposed include Siberian Husky, Fox Terrier, Old English Sheepdog, Shetland Sheepdog, Bull Terrier and Dalmatian (Cooley & Waters 2001).

Clinical signs

Interstitial cell tumour can be an accidental finding on postmortem. Feminization is rare. There is usually a scrotal or inguinal mass. On testicular ultrasound they appear as a well-circumscribed mass with hypo- and hyperechoic areas (Johnston et al 1991).

Treatment

Treatment is by castration, which is generally curative.

Seminoma

Breeds predisposed include Old English Sheepdog, Siberian Husky, Fox Terrier, Norwegian Elkhound, Great Dane, Samoyed, Bulldog, Keeshond and Weimaraner. Feminization is rare (Cooley & Waters 2001).

Clinical signs

Seminomas are bilateral in 18%, and 34% are found in cryptorchid testicles. Any association with prostatic disease and enlargement, circumanal gland hyperplasia, perianal tumours and perineal hernias is refuted (Cooley and Waters 2001). Metastatic rate is less than 10%. Sites include sub-lumbar lymph nodes, lungs, liver, spleen, adrenal glands, pancreas, central nervous system, eyes and skin. AgNOR counts are higher in dogs with metastatic seminoma compared to non-metastatic seminoma (De Vico et al 1994).

Diagnostic work-up

Work-up is as for Sertoli cell tumour.

Treatment

Treatment is by castration with a large amount of spermatic cord. Radiotherapy used in four dogs with metastatic seminoma resulted in complete remission in three dogs with no confirmed evidence of recurrence; the fourth dog died of unrelated disease (McDonald et al 1988).

Platinum-based chemotherapy used in humans and cisplatin chemotherapy have been reported in four dogs with testicular tumours (Dhaliwal et al 1999). Vincristine and cyclophosphamide was not associated with a meaningful response in one dog with cutaneous metastasis (Spugnini et al 2000).

Prognosis

Surgery is curative if there is no metastatic disease.

Other testicular tumours

Mixed germ cell–stromal tumours account for 7% of testicular tumours. Other less common tumours include haemangioma, granulosa cell, sarcoma, embryonal carcinoma, gonadoblastoma and lymphoma (LSA). Teratomas are very rare. Metastatic testicular tumours from gastrointestinal adenocarcinoma have been reported in three dogs (Esplin & Wilson 1998).

The prognosis for most patients with testicular tumours is good. The role of chemotherapy is not well defined and has been reserved for patients with metastatic seminomas where some partial responses using platinum-based chemotherapeutic agents have been seen (Dhaliwal et al 1999). For patients with bone marrow suppression the overall prognosis is guarded due to the long period of time required for bone marrow recovery, up to 5 months (Sherding et al 1981).

Scrotal tumour

The scrotum may be affected by a number of skin tumours, including mast cell tumours, SCC and haemangiosarcoma (see Chapter 20).

Tumours of the penis and prepuce

Tumours of the penis are rare. In certain parts of the world the most common tumour is transmissible venereal tumour (TVT); other tumours include papilloma, SCC and haemangiosarcoma. Other possible penile or preputial tumours include LSA, fibrosarcoma (FSA), histiocytic reticulocytoma, transitional cell carcinoma (TCC), chondrosarcoma (CSA), mast cell tumours (MCT) and papilloma.

SCC most commonly affects the glans penis and usually presents as an ulcerated mass. It is locally invasive and can metastasize to the regional inguinal lymph node.

Clinical signs

Clinical signs include haematuria or discharge from the prepuce, phimosis, increased frequency of urination or most commonly licking of the prepuce and penis due to irritation.

Physical examination

Extrusion of the penis usually reveals the presence of the tumour. Biopsies are recommended.

Treatment

With the exception of TVT that responds well to vincristine chemotherapy, the treatment of choice for penile tumours is surgical that may require partial or complete penile amputation and urethrostomy (scrotal or perineal). Regional lymph nodes (inguinal) should be removed if enlarged.

Prognosis

In general, prognosis is good for TVT. SCC usually carries a fair prognosis; haemangiosarcoma, due to the potential for metastasis, has a guarded prognosis.

Tumours of the prostate

In general, prostatic neoplasia is seen in older dogs, mean age 10 years. Most prostatic tumours in the dog are malignant and

castration provides no protective effect, meaning the development of prostatic neoplasia is not strongly influenced by male sex hormones. Common canine prostate disorders include benign prostatic hyperplasia (BPH), prostatitis, cysts, squamous metaplasia, adenocarcinoma and combinations.

Clinical signs

In most cases dogs will present with lower urinary tract signs of either haematuria or dysuria. In some cases the presenting problem will be for constipation or tenesmus. These clinical signs are indistinguishable from those of BPH. The clinical signs of dogs with prostate disease can be divided into four categories:

- Systemic signs (fever, depression, anorexia, pain, weight loss, vomiting)
- Lower urinary tract signs (constant or intermittent haemorrhagic, purulent or clear urethral discharge, recurrent urinary tract infection with dysuria, haematuria and pollakiuria, urinary retention and obstruction causing stranguria)
- Abnormalities of defecation (tenesmus, ribbon stools, large bowel diarrhoea)
- Locomotion disorders (stiff gait, weakness, lameness from pain).

Physical examination

In some instances the prostate can be palpated as a large mass in the caudal abdomen that may be painful. Palpation of the prostrate per rectum or abdominal examination should palpate for size, shape, symmetry, mobility, pain and consistency. Normal is smooth, symmetrical, non-painful, walnut-sized, with a mid-dorsal groove. Normal occupies less than 50% of the pelvic canal and is 1.1–1.3 times the length of L2 (Feeney et al 1987).

Generally dogs with neoplasia, cysts and abscesses have a larger prostate, asymmetry and possibly a nodular feel to the gland; the median raphe may not be easily discernible. Abscesses are often painful to palpate. Enlarged sub-iliac lymph nodes may also be palpated. In advanced cases there may be lumbar pain associated with metastatic lesions to the lumbar vertebrae. In contrast, BPH is characterized by a uniformly enlarged and smooth prostate.

Prostatic adenocarcinoma is the most common malignant tumour of the prostate; others include transitional carcinoma, squamous cell carcinoma and undifferentiated carcinoma. Less than 10% are adenomas, fibromas, leiomyomas and sarcomas. Prostatic neoplasia commonly has a great potential (70–90%) for secondary spread to pelvic lymph nodes, spine and pelvis, as well as direct spread into local tissue and distant sites (Cornell et al 2000). Pulmonary metastasis is more common in castrated dogs (Bell et al 1991). Skeletal metastasis is more common in young dogs (Cornell et al 2000).

Diagnostic work-up

Routine blood work is usually unremarkable. Prostate-specific antigen (PSA) is not useful in dogs; Bell et al (1995) did not detect PSA in canine serum or seminal plasma.

Serum total acid phosphatase, prostatic acid phosphatase and non-prostatic acid phosphatase were significantly higher in dogs with prostatic carcinoma compared to normal dogs or dogs with BPH in one study (Corazza et al 1994). Bell et al (1995) found that serum and seminal acid phosphatase activities did not differ significantly between normal dogs and those with prostatic diseases, or among dogs with different prostatic disorders. Serum canine prostate specific esterase (CPSE) activities were significantly higher in dogs with BPH than in normal dogs, but dogs with BPH, bacterial prostatitis and prostatic carcinoma had similar CPSE activities. Most tumours did not stain for CPSE.

Urinalysis

Culture and sensitivity should always be carried out in patients with suspected prostate neoplasia. In some cases neoplastic cells will be identified in the sediment. However, the absence of neoplastic cells does not exclude the presence of neoplasia.

Physical examination

Rectal examination should be performed annually in an attempt to detect prostatic disease early. In the neutered dog prostatic enlargement would indicate neoplastic disease, whereas in the intact male BPH must be distinguished from neoplasia.

Radiography

Plain radiographs will detect prostatomegaly, but will not distinguish the various causes of the enlargement; however, calcification within the prostate seen on plain radiographs is an indication of neoplasia rather than BPH. In some instances enlargement of regional nodes or secondary lesions within the vertebrae or pelvis may be visible. Contrast studies, both negative (pneumourethrocystogram) and positive (retrograde urethrogram), will provide supportive evidence of a prostatic tumour (periurethral asymmetry as well as narrowing, distortion or destruction of the prostatic urethra).

Ultrasound

Ultrasonography is indicated in any presentation of prostatic disease, and has the advantage of imaging the testes, urinary tract, peri-prostatic tissue and regional lymph nodes with a combination of pre-pubic and transrectal approaches. Ultrasound can differentiate the likelihood of BPH versus neoplasia, and ultrasound-guided tru-cut biopsies can be obtained for a definitive diagnosis. The former technique is superior to prostatic washes for the diagnosis of prostatic carcinoma. Ultrasound-guided FNA is easy and has 80% correlation of cytology to histological diagnosis (Powe et al 2004).

Disadvantages to ultrasound-guided biopsies are haemorrhage, damage to neurovascular supply and rectum, failure to localize the lesion and seeding infection (avoid if abscessation is suspected), as well as reports of seeding tumour (Nyland et al 2002).

Treatment

Surgery

Prostatic carcinomas have an 80% rate of metastasis at necropsy (Cornell et al 2000) and dogs mostly die or are euthanized due to urethral obstruction, rather than metastatic disease. Therefore, the main aim of surgery (or any treatment) is to relieve urethral obstruction with minimal morbidity.

Aggressive surgery (prostatectomy) is mostly not recommended as the diagnosis is made too late, quality of life is not improved, and disease is not cured. In rare cases, total transurethral prostatectomy may be indicated for early stage lesions, but it is technically difficult, most dogs (93–100%) are incontinent postoperatively, and dehiscence, stenosis, infection and sepsis are common complications.

Tube cystotomy (pre-pubic) and retained urethral Foley catheter are palliative surgical treatments which relieve outflow obstruction and prolong quality of life, with a well-informed and willing client.

Palliative urethral stenting (placed with fluoroscopic guidance) shows great promise as a minimally invasive technique with high success for relieving outflow obstruction. When prostatic urethral stenting was carried out in eight dogs with prostate cancer, six had an excellent outcome and two had mild complications. Incontinence was mild or non-existent, and no dogs were euthanized due to urinary tract obstruction (Weisse et al 2006).

Other reported minimally invasive surgical techniques such as Nd:YAG laser (L'Eplattenier et al 2006) and transurethral resection, with or without intraoperative radiation therapy (Liptak et al 2004a), have been less beneficial than stenting. Of eight dogs treated with palliative partial prostatectomy via Nd:YAG laser, three died from complications within 16 days of surgery, and the overall MST was 103 days (L'Eplattenier et al 2006). Of three dogs treated with transurethral resection and intraoperative radiation therapy, two developed urethral perforation (Liptak et al 2004a).

Radiotherapy

External beam radiation, either intraoperatively or as sole treatment, has limited palliative effect.

Radiation therapy will shrink some tumours to relieve urinary outflow obstruction and obstipation, but survival times are short. Intraoperative radiation therapy is promising if there is localized tumour. Ten dogs treated with intraoperative radiotherapy for prostate carcinoma had a median survival time of 114 days, with a complete response in five dogs who also tolerated treatment well, two dogs ultimately died of treatment complications, and three dogs had a poor response to treatment (Turrel 1987).

Chemotherapy

The Cox-2 inhibitors piroxicam or meloxicam do appear to improve quality of life for individual patients although the anti-tumour effect of these drugs is questionable. In one study, dogs receiving an NSAID had an MST of about 7 months, compared to 0.7 months for those not receiving any cancer therapy (Sorenmo et al 2004).

Platinum drugs

Unfortunately, platinum-based protocols, with or without radiotherapy, have shown no benefit to patients with prostatic carcinoma. Mitoxantrone is the standard palliative treatment in men with hormone-refractory prostatic carcinoma, although recent studies have shown a response to docetaxel (Oudard et al 2005).

Hormonal therapy

No benefit can be derived for the patient from either castration or anti-androgens, as prostatic carcinomas in the dog are independent of hormonal stimulation.

Photodynamic therapy (PDT)

PDT induced fatal prostatic necrosis (Hsi et al 2001). Another paper (Lucroy et al 2003) reported stable disease for 6 months in one dog treated with PDT.

Prognosis

In one retrospective study of 76 dogs with prostatic carcinoma the MST was 0 days with 58 euthanized at diagnosis. MST for dogs living more than 7 days was 30 days (Cornell et al 2000). Survival times for treated dogs vary with the presenting clinical signs and the treatment used. The overall prognosis is guarded.

Tumours of the kidney

Primary tumours of the kidney are rare in the dog and cat, approximately 1.7% and 2.5%, respectively (Crow 1985). Lymphoma is the most common tumour of the kidney in the cat (Mooney et al 1989) and carcinoma in the dog (Klein et al 1988). Other primary tumours include fibrosarcoma and haemangiosarcoma (Locke & Barber 2006). Metastatic renal tumours are more common than primary in the dog, and more than 90% of all renal tumours are malignant (Baskin & De Paoli 1977, Bryan et al 2006, Klein et al 1988).

No breed predisposition has been noted in canine renal tumours, but males are more commonly affected (Klein et al 1988, Lucke & Kelly 1976). Primary tumours are usually unilateral (Bryan et al 2006), although renal lymphoma in the cat can be either unilateral or bilateral (Gabor et al 1998). Primary renal tumours other than lymphoma in cats have been reported (including carcinomas, nephroblastoma, haemangiosarcoma and adenoma) (Henry et al 1999).

Clinical signs

Gross haematuria is not a consistent presenting clinical sign. Most signs are non-specific, e.g. weight loss, lethargy or anorexia (Bryan et al 2006). Other clinical signs include pain in the lumbar region, fever, abdominal distension or discomfort and pelvic limb oedema. Renal failure is rare except in cats with renal lymphoma. Early detection is recommended and any patient, particularly the older patient, presenting with haematuria should have further diagnostic tests performed immediately in the anticipation of identifying cancers at an earlier stage and improving the possibility of successful treatment. German Shepherds with renal cystadenocarcinoma may present with multiple cutaneous nodules (Lium & Moe 1985).

Diagnostic work-up

Physical examination

A large, painful kidney or in some cases caudal abdominal discomfort in the kidney region may be detected.

Haematology and biochemistry

Blood work is usually unremarkable. In some cases patients may present with polycythaemia as a paraneoplastic syndrome due to the production of erythropoietin by neoplastic cells (Gorse 1988, Henry et al 1999, Peterson & Zanjani 1981). A biochemistry profile should be evaluated for renal compromise and occasionally hypercalcaemia may be present as a paraneoplastic syndrome. All cats with lymphoma

should have their feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) status checked.

Urinalysis

Proteinuria and haematuria are common findings; the presence of diagnostic neoplastic cells is rare.

Imaging

Plain radiographs may demonstrate renomegaly. Assessment of renal function via intravenous urography (IVU) is beneficial but in most cases evaluation of the kidneys via ultrasound is the primary diagnostic tool. Renal ultrasonography enables the architecture of the kidneys to be examined as well as assessing the patient for regional extension of the tumour, either by invasion into the vena cava or spread to local lymph nodes.

MRI/CT scans are valuable when local invasion into the vena cava is suspected prior to surgical intervention. The functional status of the remaining kidney should be evaluated before nephrectomy is performed.

Treatment

Surgery

Unilateral disease is best treated with nephrectomy, to include ureter and retroperitoneal muscle if involved (**Figure 17.9**).

Chemotherapy

The role of chemotherapy in non-lymphoid renal tumours has not been well evaluated and, as in humans, renal carcinoma appears to be chemoresistant. For renal lymphoma, the treatment of choice is chemotherapy (see Chapter 22).

Prognosis

Renal carcinoma

Renal carcinoma occurs in older male, medium to large breed dogs. It can invade the caudal vena cava, and can cause paraneoplastic polycythaemia and neutrophilic leucocytosis. Metastatic disease is common in dogs, with pulmonary metastases in 16% of dogs at diagnosis and in 77% at time of death (Bryan et al 2006). The metastatic rate for cats with primary renal neoplasia (excluding lymphoma) with complete staging was 64% and 100% for transitional cell carcinomas (Henry et al 1999).

Because renal carcinomas are chemoresistant, stage and grade are important; patients with regional and distant metastase have a poor median survival time. Poor survival time reflects advanced stage, difficulty in complete excision and high metastatic rate (Klein et al 1988). Most dogs with primary renal adenocarcinoma live 6–8 months if operable (Klein et al 1988), though there have been reports of survival up to 4 years (Lucke & Kelly 1976). Bryan et al (2006) reported a median survival of 16 months for carcinomas, 9 months for sarcomas and 6 months for nephroblastomas, with surgery the only treatment.

Bilateral renal cystadenocarcinoma

This rare tumour is seen in German Shepherds as part of the syndrome of nodular dermatofibrosis. Slowly progressive, with metastasis in up to 43% of cases (Lium & Moe 1985), death results from renal failure, secondary skin infections and metastatic disease (Moe & Lium 1997).

Nephroblastoma (Wilm's tumour)

Wilm's tumour is the most common renal tumour in young dogs, with a mean age of 4 years, but is often seen in dogs less than 1 year of age. This embryonal tumour may be present in one pole of the affected kidney, and may demonstrate primitive epithelial and mesenchymal tissues such as vestigial tubules, muscle, cartilage and bone (White 2003). Metastasis is reported in 65% of patients and usually less than 12-month survival time when treated with nephrectomy ± chemotherapy (Coleman et al 1970, Frimberger et al 1995), with one report of survival more than 25 months (Seaman & Patton 2003). However, nephrectomy may ensure prolonged survival or cure in some cases (Seibold & Hoerlein 1957, Simpson et al 1992).

Benign renal tumours

Except for haemangioma, these are usually asymptomatic, e.g. fibroma, myxoma, lipoma, mixed tumours, leiomyoma, adenoma and papilloma.

Renal lymphoma

Stage, degree of response, FeLV status and renal function are prognostic factors for cats with renal lymphoma. MST is 408 days if complete response is achieved, 75 days with partial response, 267 days if FeLV positive and 610 days if FeLV negative (Mooney et al 1989). Patients with azotaemia that does not resolve after induction chemotherapy have a poor prognosis (see Chapter 22). Renal lymphoma is rare in the dog.

Mesenchymal renal tumours

These tumours have an MST of 9 months postsurgical excision (Bryan et al 2006). Renal haemangiosarcoma is a rare anatomical variant of haemangiosarcoma with improved survival times over splenic disease (Locke & Barber 2006).

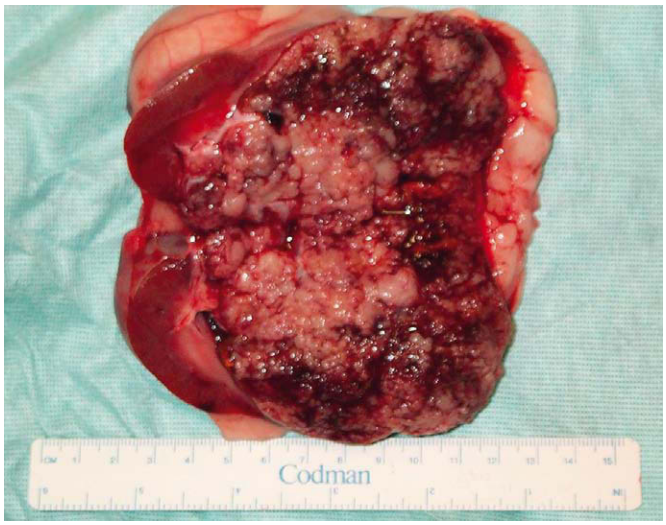

Figure 17.9 Renal carcinoma (sectioned). (Courtesy R Straw.)

Tumours of the ureter

Primary tumours of the ureter are extremely rare in both the cat and the dog and are typically leiomyoma/sarcoma or transitional cell carcinomas. The ureters can be involved due to invasion by either renal or bladder tumours. Obstruction of the ureter with tumour leads to the development of hydroureter

and hydronephrosis in the affected kidney; however, providing only one ureter is affected, signs of renal failure may not be apparent and signs similar to obstruction due to urolithiasis may be seen, i.e. lethargy, lower back pain, anorexia.

Diagnostic work-up

An IVU will allow precise evaluation of a ureteral neoplasm in conjunction with abdominal ultrasound to evaluate the ipsilateral kidney.

Treatment

The treatment of choice is ureteronephrectomy. The functional status of the contralateral kidney should be evaluated prior to surgery. These tumours are rare and no chemotherapy protocols have been described.

Prognosis

The prognosis is guarded for malignant tumours; however, leiomyosarcomas are slow to metastasize and therefore excision would carry a fair prognosis. The worst prognosis would be expected for TCC of the ureter because of its higher metastatic potential.

Tumours of the urinary bladder

The urinary bladder is the most common location of canine urinary tract tumours, and accounts for approximately 1% of all canine neoplasms (Crow 1985, Mutsaers et al 2003). The most common tumour is transitional cell carcinoma, which accounts for approximately 90% of canine bladder tumours (Norris et al 1992, Rocha et al 2000, Valli et al 1995). Other malignant tumours seen in the urinary bladder include adenocarcinoma, sarcomas, haemangiosarcomas and lymphomas (Benigni et al 2006, Liptak et al 2004b, Norris et al 1992, Olausson et al 2005, Rocha et al 2000, Valli et al 1995). Benign tumours include polyps (Martinez et al 2003) and leiomyomas (Heng et al 2006) (see Table 17.5).

Transitional cell carcinoma (TCC)

TCC is typically invasive and is most often located in the trigone region of the bladder (**Figure 17.10**). These tumours are malignant and will metastasize to the local lymph nodes and lungs, with about 30% of patients having metastases at the time of diagnosis (Knapp et al 2000).

Signalment

TCC is found typically in middle-aged to older dogs, with an overall incidence greater in females than males (Knapp et al 2000, Mutsaers et al 2003, Norris et al 1992). Breeds overrepresented include West Highland White Terrier, Jack Russell Terrier, Beagle and Scottish Terrier (Sapierzyński et al 2007).

Clinical signs

The most common presenting clinical sign is haematuria that may be temporarily responsive to antibiotics. Other clinical signs seen are consistent with lower urinary tract signs including stranguria and dysuria. In extreme cases patients may present with anuria due to complete obstruction of the urethra with tumour. In some cases patients may present in renal failure due to obstruction of the ureters at the level of the trigone. It is imperative that older patients with haematuria receive an appropriate work-up rather than being kept on antibiotics as unfortunately delay in diagnosis often means that these tumours are diagnosed only when they are extremely advanced. High concentrations of basic fibroblast growth factor have been found in the urine of dogs with cancer and the hope is that such assays may lead to earlier detection of bladder cancer (Allen et al 1996).

Staging

Staging of bladder tumours is according to the TNM system (Table 17.6).

Table 17.5 Tumours of the canine urinary bladder

Benign	Malignant
• Leiomyoma • Fibroma • Haemangioma	• Transitional cell carcinoma • Adenocarcinoma • Leiomyosarcoma • Haemangiosarcoma • Lymphoma • Squamous cell carcinoma • Rhabdomyosarcoma (embryonal) • Fibrosarcoma

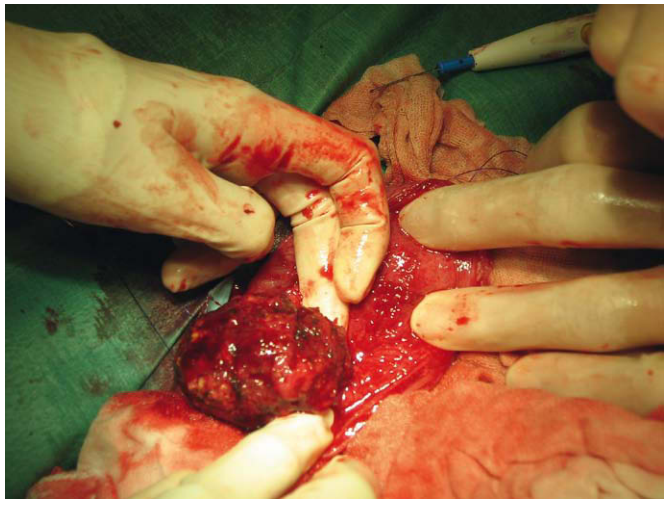

Figure 17.10 Bladder transitional cell carcinoma.

Table 17.6 TNM classification of canine bladder tumours

Tumour	Node	Metastasis
T0: no evidence of tumour	N0: no nodal involvement	M0: no distant metastasis
T1: superficial tumour	N1: regional node involvement	M1: metastasis present
T2: invading bladder wall	N2: regional and juxtaregional node involvement	
T3: tumour invading regional organs		

Diagnostic work-up

Bladder tumours are most routinely diagnosed via ultrasound and ultrasound-guided biopsies have a sensitivity and specificity of 90%. Ultrasound-guided or blind catheter biopsies are also useful, and avoid the complication of tumour seeding, although care must be taken not to rupture the urethra or bladder neck (Holt et al 1986, Lamb et al 1996).

Cystoscopy, when available, has a specificity and sensitivity of close to 100%.

Contrast studies are valuable to delineate any intraluminal mass. Care should be taken when aspirating any bladder mass as TCC is known for 'seeding' along the needle tract (Nyland et al 2002, Vignoli et al 2007).

TCC usually arises in the trigone area of the bladder so the ureters and kidneys should be evaluated for hydroureter and/or hydronephrosis.

Treatment

Surgery

Partial cystectomy alone has been reported to result in an MST of 3–6 months. Stone et al (1996) reported 11 dogs with bladder neoplasia treated by partial cystectomy, with 5 dogs euthanized 2–7 months after surgery, 6 dogs surviving at least 1 year and 2 of these alive at 17 and 27 months.

In general, tumour-free margins are impossible (Knapp et al 2000). Failure is attributable to local recurrence due to the seeding of tumour throughout the urinary bladder and both regional and distant metastasis.

Chemotherapy

In humans with TCC the platinum-based drugs have been used with good success rates. However, in humans, early detection and more superficial disease result in better outcomes than in veterinary patients. Approximately 20% of human patients have invasive TCC and do not respond well to platinum-based chemotherapy; unfortunately, dogs with TCC have tumours similar to this small percentage of human patients.

A number of studies have evaluated the efficacy of chemotherapy in dogs with non-resectable TCC. The response rate for patients treated with cisplatin was <30% (Chun et al 1996) and the potential nephrotoxicity has meant that cisplatin is not currently recommended. The cisplatin analogue carboplatin has been examined as an alternative to cisplatin. Unfortunately, the response rates were poor, with one study reporting no survival benefit from carboplatin chemotherapy when used as sole agent (Chun et al 1997).

The cyclooxygenase inhibitor piroxicam (Feldene) was shown in a number of studies to improve quality of life for patients with TCC. The main side effects included gastrointestinal irritation and sub-clinical renal toxicity. At the recommended dose (0.3 mg/kg once daily) the median survival time was 181 days (Knapp et al 1994). Clients report an improvement in clinical signs with an improved quality of life for these patients.

The combination of cisplatin and piroxicam resulted in clinical nephrotoxicity and is not recommended for the treatment of TCC (Chun et al 1996, Mohammed et al 2003). Carboplatin and piroxicam resulted in remission in about 40% of patients with median survival of 161 days (Boria et al 2005). Mitoxantrone, a drug related to doxorubicin, has been combined with piroxicam and in one study the overall survival time was increased from 181 days with piroxicam alone to 291 days on combination therapy in 48 dogs (Henry et al 2003). The protocol consisted of four cycles of mitoxantrone (5 mg/m^2 intravenously) at intervals of 3 weeks, with piroxicam administered at the standard dose throughout.

In general, the protocol was well tolerated with subjective improvement in 75% of the treated dogs. Diarrhoea and azotaemia were the most common side effects. Currently, for dogs with non-resectable TCC, the combination of mitoxantrone and piroxicam, and piroxicam alone, are the primary treatment options. Meloxicam has also been shown to have a similar effect on bladder tumours as piroxicam and is often substituted for it.

Radiotherapy

Radiotherapy intraoperatively, either as a single treatment or as part of a fractionated programme, has been shown to give good long-term local control; however, the side effects of treatment – primarily bladder fibrosis and urinary incontinence – have meant that this treatment modality is rarely carried out in veterinary medicine. Cisplatin in combination with radiotherapy did not show any advanced survival over radiotherapy alone (Walker & Breider 1987).

Tumours of the urethra

Neoplasia of the urethra is uncommon in both the dog and cat. In the female dog the major differential is granulomatous urethritis. Urethral neoplasia is seen most commonly in the older female, with no known breed predisposition. TCC is the most common tumour of the proximal third of the urethra, and squamous cell carcinoma the distal portion of the urethra and urethral tubercle. These tumours are invasive and will metastasize to local lymph nodes and pelvic organs.

Very rarely sarcomas of the urethra will be seen (**Figure 17.11**). Granulomatous urethritis is an important differential diagnosis. Multiple chondrosarcomas in the urethra of a dog have been reported (Davis & Holt 2003).

In 20 cases of canine primary urethral neoplasia, SCC was the most common. The most useful diagnostic method was pneumocystography-cystography, with voiding urethrography. Metastasis occurred in 6 of the 20 dogs (Tarvin et al 1978).

Clinical signs

These are consistent with lower urinary tract signs, i.e. dysuria, pollakiuria, haematuria and stranguria.

Physical examination

Many of these tumours are palpable, either on rectal or vaginal examination. They may be palpated as either a discrete mass or diffuse swelling of the urethra.

Diagnostic work-up

Endoscopy and positive contrast studies are the most useful diagnostic procedure. Surgical exploration and treatment may be necessary if imaging is not helpful. Abdominal ultrasound and thoracic radiographs are performed prior to extensive surgery for staging purposes.

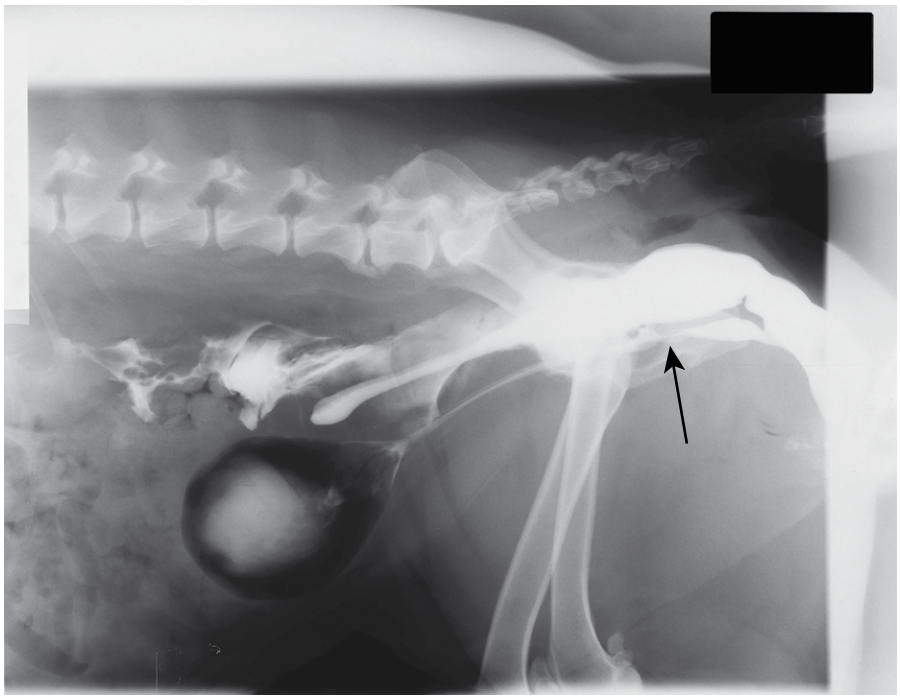

Figure 17.11 Contrast study in a dog with a urethral sarcoma.

Treatment

Surgery

An incisional biopsy is important to rule out granulomatous urethritis before extensive surgery or euthanasia. Incisional biopsies may be obtained surgically or using endoscopic biopsy forceps. For definitive surgery, a combination of perineal, pelvic or abdominal surgical approaches may be required, depending on tumour location. Contrast radiographic studies are useful to help plan the surgical approach. Urinary diversion techniques may be required if the urethra cannot be reconstructed. Urethral stenting may be useful for non-resectable tumours, e.g. TCC.

Chemotherapy

TCC of the urethra responds as for bladder TCC.

Feline urinary tumours

Bladder tumours

Bladder tumours in cats are rarely reported, but seem to be different from those in dogs in that only 15 of 27 cases reported were carcinomas, the remainder were mesenchymal (leiomyoma, leiomyosarcoma and haemangiosarcoma) or lymphoma. Four of nine cats treated with partial cystectomy had mesenchymal tumours, and lived >6 months after surgery (Schwarz & Willer 1989).

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Tumours of skin and subcutaneous tissues

Tumours of the skin and subcutaneous tissues are the most common tumours in the dog, accounting for one-third of all neoplasms (Bostock 1986, Brodey 1970, Finnie & Bostock 1979, Rothwell et al 1987). In the cat, skin neoplasms are second in frequency only to lymphoid tumours (Vail & Withrow 2007). Mast cell tumours (MCT) are the most common skin tumour in the dog, and second most common in the cat (Miller et al 1991) (see Chapter 19). Approximately 20–30% of skin tumours in dogs are malignant, compared to 50–65% in the cat (Kaldrymidou et al 2002, Mukaratirwa et al 2005). Generally, cutaneous tumours occur in older animals. Long-term effects of sunlight result in solar dermatosis, leading to documented increases in cutaneous haemangioma, haemangiosarcoma (HSA) and squamous cell carcinoma (SCC) in dogs, and SCC in cats (Dorn et al 1971, Knowles & Hargis 1986, Madewell 1981, Nikula et al 1992).

Clinical signs

The presence of a lump or bump requires investigation. It is important to establish the time the lump has been present and whether or not it has changed or grown in size since it was first noticed, therefore a thorough history and clinical examination are essential in the diagnostic evaluation of any patient with a cutaneous mass.

Three-dimensional calliper measurements give an objective assessment of change and their use should be encouraged. All cutaneous lumps should undergo fine needle aspirate (FNA) as the first diagnostic step, as well as any enlarged lymph nodes. Cytological examination of a lump will help to determine non-neoplastic (hyperplasia, infection or cyst) from neoplastic and in some cases give preliminary identification to a neoplastic growth (e.g. mast cell tumour).

CANINE TUMOURS

Tumour-like lesions

Several types of skin lesions mimic neoplasms, including epidermoid cysts, dermoid and follicular cysts.

Epidermoid cysts (epidermal inclusion cyst, sebaceous cyst) are round to oval, firm to fluctuating, smooth, well-circumscribed lesions that are common in dogs but rare in cats. They are more common on extremities. These masses may contain grey to white-brown cheesy material with bits of hair shafts, usually covered by intact epithelium.

Dermoid cysts are similar, but more complex in that they are often multiple, deeper and can be interconnecting. They appear to be congenital or hereditary in Boxers, Rhodesian Ridgebacks, and Kerry Blue Terriers (Hofmeyer 1963). They are usually found on the dorsal midline, neck and scrotum. Some can extend to the level of the meninges and be continuous with the subarachnoid space. The prognosis is generally excellent with adequate surgery.

Nodular dermatofibrosis (collagenous nevi)

This is an unusual syndrome in German Shepherd (GSD) dogs, characterized by the development of numerous cutaneous nodules. Histologically, they appear as hyperplastic dermal collagen. Almost all cases are associated with multiple bilateral renal cysts that progress to cystadenocarcinomas with metastatic potential. Dogs eventually succumb to renal failure or widespread metastasis. No effective treatment exists (Vail & Withrow 2007).

Tumours of the skin and subcutaneous tissues can be divided into four categories although some overlap may occur:

- tumours of epithelial origin
- round cell tumours
- tumours of mesenchymal origin
- tumours metastatic to skin.

Tumours of epithelial origin

Papillomas

These tumours are common in the dog, very rare in the cat. In young dogs they are associated with a DNA virus that is contagious from dog to dog, and usually spontaneously resolve in a few months. These wart-like lesions often affect the mouth, eyelids, head, and feet. An intact immune system is important for disease regression.

A second type of papilloma is seen in the older dog. This is usually solitary and not thought to be associated with a virus. The prognosis is excellent with surgical excision or cryosurgery (Vail & Withrow 2007).

Squamous cell carcinoma (SCC)

Squamous cell carcinoma usually arises in unpigmented or lightly pigmented skin and is often related to solar exposure ('actinic SCC') (**Figure 18.1**). The most common cutaneous locations in the dog are the nail bed, scrotum, nose, legs and anus. For dogs with lightly pigmented skin, SCC can be seen

on the flank and abdomen (Hargis et al 1977). Golden Retrievers appear to be over-represented with SCC of the nose (Bosward et al 2004, Gallegos et al 2007). Treatment depends on size, location and degree of invasiveness of the tumour (also see Chapter 13).

Staging of the patient with SCC requires evaluation of the sentinel node (FNA or excisional biopsy) and thoracic radiographs/CT. In general, the metastatic potential of cutaneous SCC is low, with pulmonary metastases reported infrequently.

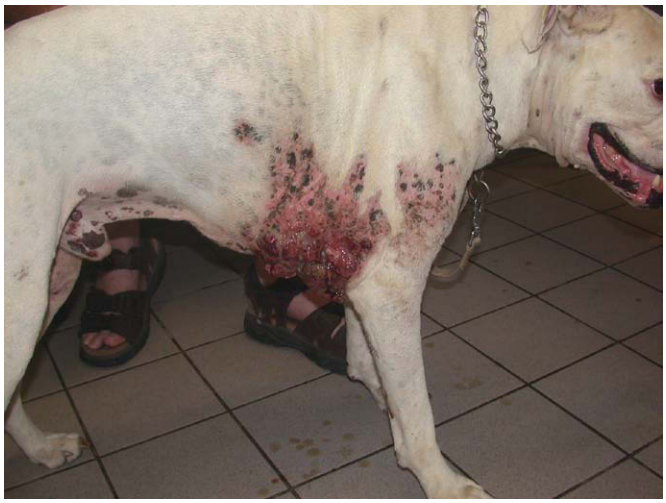


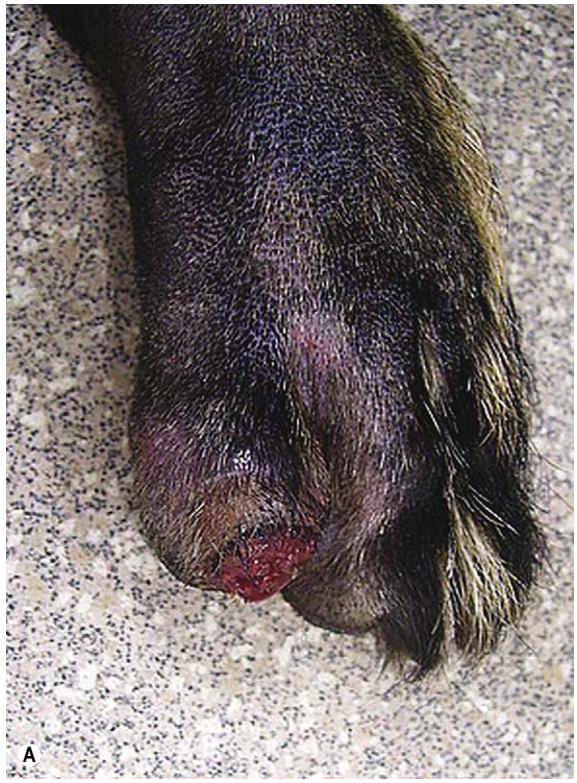
Figure 18.1 Cutaneous squamous cell carcinoma in a light-skinned dog. (Courtesy R Straw.)

Treatment

Small superficial lesions may be amenable to photodynamic therapy (PDT) or cryotherapy (Chapter 8). Large or invasive tumours require surgery, radiotherapy or a combination of the two. Large, locally invasive lesions have a poorer prognosis, due to the likelihood of recurrence. The success of local control or cure of SCC of the canine nasal planum is dependent upon the treatment used and the extent of tumour at the time of diagnosis (Chapter 13).

Subungual SCC

This is a common tumour in the dog and deserves special mention as they can often be misdiagnosed, along with the other common subungual tumour, melanoma, as infection. SCC is the most common subungual neoplasm and accounts for between 30 and 50% of all subungual tumours (Henry et al 2005, Marino et al 1995, O'Brien et al 1992, Wobeser et al 2007) and typically presents as a nail bed (paronychia) infection that does not respond to antibiotic therapy. It is seen most frequently in large breed dogs (~75%), with black dogs accounting for two-thirds of the cases (Vail & Withrow 2007). It arises from the subungual epithelium and often causes lysis of third phalanx (**Figure 18.2**).



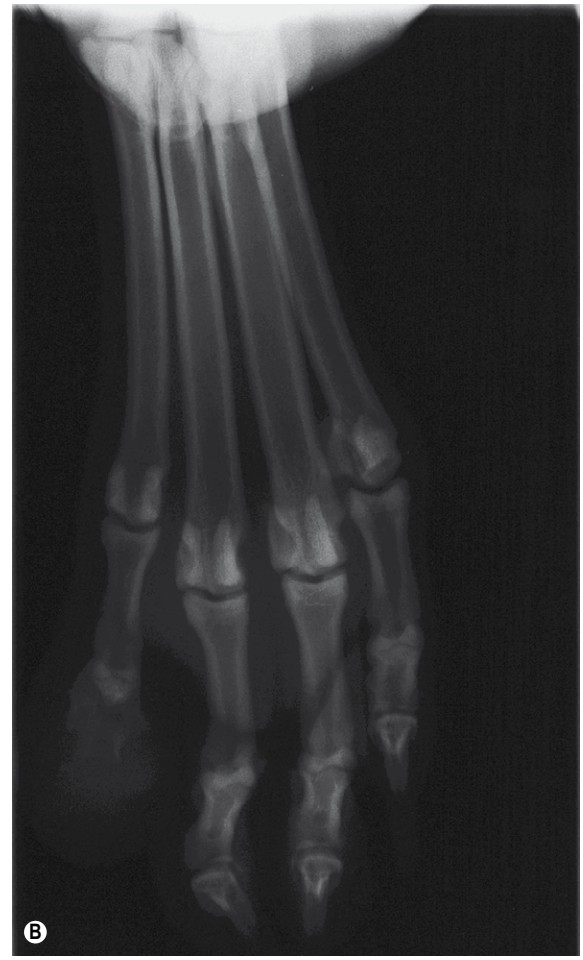


Figure 18.2 (**A**) Subungual squamous cell carcinoma in a dog. (**B**) Radiograph showing digital lysis (same patient).

Diagnostic work-up for the patient with persistent paronychia should include digital radiographs to check for evidence of lysis. If SCC is confirmed on a biopsy, evaluation of the regional lymph node and thoracic radiographs are indicated. The treatment of choice is digital amputation and with adequate margins the overall prognosis is fair. If a surgical margin cannot be achieved due to either the size or location, radiotherapy is the alternative treatment option, preferably in combination with surgery or in some cases as sole treatment.

Typically SCC is locally invasive but the majority of these tumours do not metastasize (Marino et al 1995). Multiple digits can be involved and unfortunately if digital amputation is not possible, this warrants a poor prognosis. Liptak et al (2005) reported good function and tumour control with amputation of both central weight-bearing digits (digits 2 and 3). In the authors' experience, small dogs can function with amputation of most digits on a single limb.

The role of chemotherapy has not been established in the management of canine SCC and is currently not recommended. For superficial solar-induced and pre-neoplastic skin lesions, retinoids (etretinate) have been used (Marks et al 1992). Etretinate is a valid option for treatment of solar-induced pre-neoplastic lesions; however, the cost of treatment can be considerable. It may be considered for multifocal superficial disease not easily managed by other means of local therapy. PDT should be considered for canine patients with superficial disease (see Chapter 8).

Basal cell tumours (including basal cell carcinomas, basal cell epitheliomas and basaloid tumours)

These tumours are almost always benign and the most common locations are found on the head, neck and shoulder regions. They are solitary, well-circumscribed, firm, hairless, dome-shaped masses and can be pigmented, cystic, solid or ulcerated. Surgical excision is almost always curative. In patients where complete surgical excision cannot be guaranteed, radiotherapy is effective in local control.

Sebaceous gland tumours

These are frequently seen in older dogs and should be distinguished from sebaceous gland hyperplasia. The most common sebaceous gland diagnosis is hyperplasia, likely forming a continuum with eventual transformation to sebaceous adenoma and finally adenocarcinomas (Vail & Withrow 2007).

Sebaceous gland adenomas

These are benign tumours commonly seen in Cocker Spaniels and Poodles. They appear wart-like and are often pedunculated and frequently occur in multiples. If traumatized, they should be surgically excised; the prognosis is excellent.

Sebaceous gland adenocarcinomas

These are relatively uncommon malignant tumours of sebaceous gland origin. They are locally invasive, but with low metastatic potential. The treatment of choice is surgical excision with clean margins; in patients where this cannot be guaranteed, radiotherapy is indicated. The efficacy of chemotherapy has not been proven.

Sweat gland tumours

These uncommon tumours of epithelial origin arise from either the apocrine sweat glands that make up the majority of the tubular skin glands or eccrine sweat glands that are found in the footpad. Cysts of apocrine sweat glands are benign lesions and are common. Adenomas and adenocarcinomas are rare, with adenocarcinomas being more frequently seen. With timely, adequate local treatment, the distant metastatic rate is low, despite fairly common local tumour invasion, particularly into local lymphatics (Kalaher et al 1990, Simko et al 2003).

Post-excisional median survival of dogs with apocrine sweat gland adenocarcinomas was 30 months at the time of survey, and intravascular invasion may be an important indicator of potential systemic metastases (Simko et al 2003).

The treatment of choice is surgical excision with adequate margins. In patients where complete excision cannot be guaranteed, radiotherapy is indicated and is usually necessary in patients with eccrine tumours to prevent local recurrence. The efficacy of chemotherapy has not been proven.

Hepatoid gland tumours (perianal gland tumours)

These tumours arise from the circumanal glands and are modified sebaceous glands. They are discussed in Chapter 15.

Ceruminous gland tumours

These tumours arise from the modified apocrine sweat glands found in the external ear canal. For a full discussion of these tumours, see Chapter 13.

Anal sac adenocarcinoma

These tumours arise from the apocrine glands of the anal region. For a full discussion of these tumours, see Chapter 15.

Intracutaneous cornifying epithelioma (keratoacanthoma)

This is a benign epithelial proliferation arising from between hair follicles that is seen only in the dog. It usually affects dogs less than 5 years old and is more commonly seen in males than females. Predisposed breeds include Norwegian Elkhound, Keeshond and GSD. Surgical excision offers an excellent prognosis for solitary tumours. Multiple small lesions can be treated with cryosurgery. Long-term treatment with synthetic retinoids may be successful (Vail & Withrow 2007).

Tumours of the hair follicles: trichoblastomas, trichoepithelioma and pilomatrixoma

Trichoblastomas arise from the primitive hair germ epithelium; trichoepitheliomas arise from the follicular sheath and are more common; pilomatrixomas arise from the hair matrix. All generally have an excellent prognosis following surgery. However, metastasis can occur from malignant pilomatrix-

oma and from clear cell adnexal carcinoma/follicular stem cell carcinoma.

Round cell (discrete cell) tumours (round cell cytological appearance but varying histogenesis)

Round cell tumours are so called because they appear to be individually oriented, round cells with no association to other cells on the slide. The round cell tumours include lymphoma, plasmacytoma, MCT, histiocytoma, transmissible venereal tumours (TVT) and neuroendocrine tumours. Melanomas and basal cell tumours can appear to be discrete cell tumours.

Cutaneous plasma cell tumours

Referred to as extramedullary plasmacytic tumours, they typically occur in older, usually large breed dogs. On histology they are composed of round cells consistent with plasma cells. Systemic involvement is rare as they are almost always benign. Infrequently, multiple myeloma may develop in these patients years after the primary plasmacytoma has been eliminated (Lester & Mesfin 1980).

In general, the prognosis is excellent and the treatment of choice depends on the size, location and availability of treatment. Surgical excision is usually recommended; however, for a very small tumour on the end of the nose or adjacent to the footpad, surgery would be disfiguring so other options include chemotherapy (cyclophosphamide/melphalan and prednisolone) or radiotherapy. The former is effective on small lesions; however, if a complete response is not achieved, then it may shrink the tumour prior to surgery. Radiotherapy provides excellent control for tumours not amenable to surgery and for large intra-oral tumours will shrink them, allowing a smaller surgery to be performed.

Cutaneous lymphoma

Non-epitheliotrophic lymphoma

Cutaneous lymphoma has always presented a treatment challenge because of the general poor response to standard chemotherapy protocols. The poorest responses were seen in patients with cutaneous T-cell lymphoma (CTCL). Immunophenotyping is recommended for all malignant cutaneous round cell tumours because it can be difficult to distinguish lymphomas from histiocytic tumours based on morphology alone, and with lymphoma immunophenotype is a prognostic indicator. CCNU is the drug of choice for cutaneous lymphomas. It will induce good partial to complete remission in many cases, although the response is transient with progression of disease inevitable (**Figure 18.3**). For a full discussion of lymphoma, see Chapter 22.

Epitheliotropic lymphoma (ELSA)

ELSA, although an uncommon clinical disease, is the most common variant of CTCL. Historically it has been referred to as 'mycosis fungoides' (MF) because of its similarities to MF in humans. CTCL typically expresses the T-cell markers CD3 and CD8, and ELSA is characterized by lymphocyte epitheliotropism throughout all stages of the disease.

The clinical presentation and progression of ELSA can be extremely variable. In some patients the diagnosis of ELSA may take many months as the patients present with 'dandruff' and are treated with medicated baths for dry skin. Eventually, these may progress to solitary patches (**Figure 18.4**), plaques or nodules, generalized erythema and scaling with mucocutaneous involvement. Most dogs affected with ELSA will become extremely pruritic. Rarely, patients may present with solitary oral lesions.

In patients with these clinical signs a biopsy is required for diagnosis. The histopathological changes seen in a biopsy are characteristic for ELSA and distinct from other cutaneous lymphomas. The unique characteristic of ELSA is the presence of Pautrier's microabscesses (collections of neoplastic lymphocytes around cutaneous dendritic cells); the neoplastic cells are confined to the epidermis and show tropism for the hair follicles and apocrine sweat glands. Advanced disease is characterized by lymphadenopathy or circulating T cells in the peripheral blood (Sézary syndrome); the latter is extremely uncommon.

The variable clinical behaviour of ELSA is well documented, with a range from mild indolent disease to a rapidly progres-

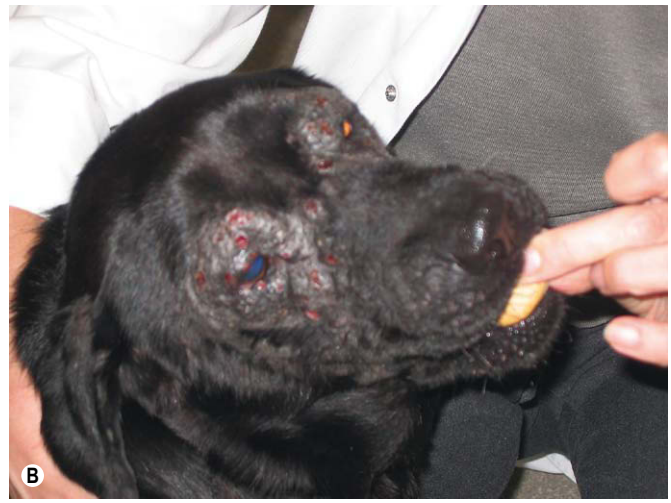


Figure 18.3 (**A**) Cutaneous lymphoma before CCNU chemotherapy. (**B**) Same dog 21 days after first cycle of CCNU.

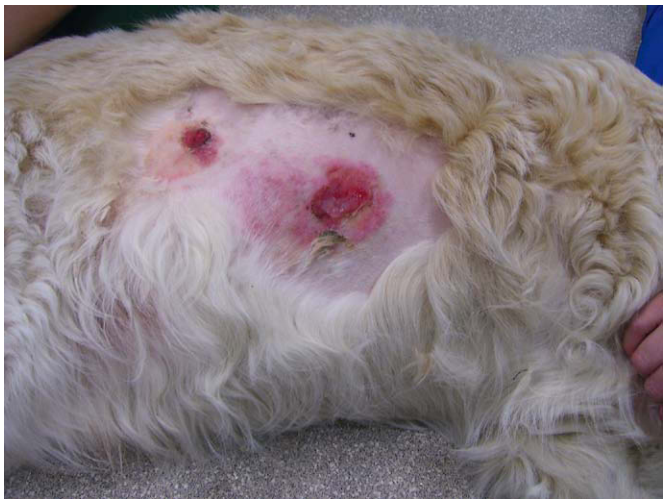


Figure 18.4 Epitheliotropic lymphoma.

sive and fatal condition with survival times of only a few months. The more advanced the disease at the time of diagnosis, especially with lymph node or systemic involvement, the more guarded the prognosis. A number of treatment options are available for patients with ELSA and include surgical excision or external beam radiation for isolated lesions. The latter would be considered the treatment of choice for solitary oral lesions and the authors currently recommend three to four treatments at 500 cGy/treatment (6 MV) at weekly intervals.

Other topical treatments for ELSA have been used that include nitrogen mustard (however, this requires repeated application by the client with the associated risk of exposure to the chemotherapeutic agent by others in addition to the patient), and methoxsalen combined with UV light. Prednisolone is beneficial in the early stages of the disease and reduces pruritus for patients with more advanced disease.

For those patients with more significant disease and not suitable for localized treatment, a number of approaches have been tried and although the gold standard of treatment has not been established, CCNU is currently the drug of choice. To compare CCNU with other treatment options a number of studies have evaluated this drug (Risbon et al 2006, Williams et al 2006). In these studies the response rate was from 78 to 83% compared to <50% with other earlier treatments including retinoids (White et al 1993), ciclosporin, fatty acids, dacarbazine, PEG L-asparaginase and pegylated doxorubicin (Vail & Young 2007). The duration of response was variable, as were the number of cycles of drug required to induce and maintain the response. The authors currently recommend three cycles at 3-weekly intervals at a dose of 60 mg/m^2 (this may need to be adjusted depending on the degree of myelosuppression). After three cycles the patient is evaluated and treatment modified according to response.

Histiocytomas and cutaneous manifestations of histiocytic disease

For a more detailed discussion of histiocytic cell derivation, see Chapter 20. Briefly, canine histiocytic disease complex can be divided into a number of categories and in some cases it can be difficult to distinguish between them:

- cutaneous histiocytoma
- cutaneous histiocytosis
- systemic histiocytosis
- histiocytic sarcoma (see Chapter 20)
- disseminated histiocytic sarcoma (malignant histiocytosis) (see Chapters 20 and 23).

Cutaneous histiocytoma

This tumour is common in the dog though very rare in other species. Arising from the macrophage cells in the skin, histiocytomas are seen predominantly in young dogs but can be seen at any age, with a second peak in middle age. Usually they are solitary, fast-growing lesions, which can be diagnosed by FNA. Although rapid growth and high mitotic index are suggestive of malignancy, these tumours are benign in nature. They usually regress in a few months. The prognosis is excellent.

In very rare cases these tumours have been shown to behave aggressively, with local recurrence, invasion and metastasis. They are radiation sensitive, but the indication for this modality is extremely rare. The occurrence of multiple cutaneous histiocytomas is also rare and is usually seen in older dogs. In most cases immunohistochemistry is required to differentiate these tumours from cutaneous lymphoma. Delayed regression may occur (up to 10 months) and may be more common in Shar Peis (Moore & Affolter 2005).

Cutaneous histiocytosis (CH)

CH may occur as either single or multiple lesions, which may wax and wane and in some cases spontaneously regress. Corticosteroids may be of some benefit, but as they rarely induce a remission, additional immunosuppressive treatment may be necessary (ciclosporin A) (Mays & Bergeron 1986, Palmeiro et al 2007).

Systemic histiocytosis (SH)

This is a familial disease in Bernese Mountain Dogs (BMD) and is occasionally seen in other breeds. The cutaneous manifestations are identical to CH but involvement of mucous membranes (ocular and nasal) and a variety of other organs (lymph nodes, lung, bone marrow) distinguish it from the more benign CH. This is a progressive disease that requires constant immunosuppression (Moore & Rosin 1986, Rosin et al 1986).

Histiocytic sarcoma (HS)

Histiocytic neoplasia that originates at a single site is known as localized HS (see Chapter 20). This is commonly found on the extremities or associated with joints, and should be treated early with surgical excision or amputation of the affected leg. Disseminated HS occurs when the tumour has spread beyond the regional lymph node and is more likely to occur when HS arises internally, e.g. spleen or lung (Affolter & Moore 2002). Disseminated HS was previously known as malignant histiocytosis (MH).

Primary HS can occur in a number of organs in addition to the skin, subcutis and periarticular tissues, including spleen, lymph node, lung, bone marrow and aggressive bone lesions

associated with a soft tissue mass (Affolter & Moore 2002, Cruz-Arámbulo et al 2004, Ramirez et al 2002, Schultz et al 2007, Spangler et al 1994). Secondary sites include liver and lung (with splenic primary) and hilar lymph node (with lung primary). The central nervous system (CNS) can be involved as either a primary or a secondary site.

For patients with periarticular HS the initial presenting sign is usually lameness and the diagnostic evaluation is similar to patients with synovial cell sarcomas. However, with HS, in addition to evaluation of regional lymph nodes and thorax, an abdominal ultrasound/contrast-enhanced CT is advised to rule out disseminated HS. Regenerative and non-regenerative anaemias may also be seen in patients with disseminated HS.

Localized HS affecting the skin and subcutis appears as a solitary cutaneous to subcutaneous lump that is non-painful and may be growing rapidly. FNA shows a population of round cells and biopsy is required for diagnosis. In many instances immunohistochemistry is required for identification of histiocytic tumours from cutaneous lymphomas.

Transmissible venereal tumour (TVT)

This round cell tumour is typically associated with the reproductive area but lesions can be seen in other locations, primarily the mouth as a result of grooming. Tumours typically are friable and have a cauliflower-like appearance. The treatment of choice is vincristine chemotherapy, typically given once weekly for up to five treatments at a dose range of 0.5–0.7 mg/m^2. In rare instances of drug resistance, or in patients that cannot tolerate vincristine, radiotherapy is successful (Nak et al 2005, Rogers et al 1998).

Mast cell tumour (MCT)

For a detailed discussion of mast cell tumour, see Chapter 19.

Cutaneous neuroendocrine (Merkel cell) tumours

Merkel cells are thought to be skin mechanoreceptors. These tumours are rare in dogs and cats. They appear to be behaviourally benign in the dog and can be treated successfully with surgical excision (Brodey 1970). In cats, one of two cases reported metastasized (Bagnasco et al 2003, Patnaik et al 2001).

Tumours of mesenchymal origin

This group of tumours primarily consists of the soft tissue sarcomas in addition to melanomas.

Lipoma/infiltrating lipoma/liposarcoma

Lipomas are common, benign proliferations of fatty tissue, seen most commonly in older large breed dogs, e.g. Labrador Retrievers, Dobermans and Weimaraners. Although benign they should be removed if they are growing quickly, or are in a location that may cause discomfort to the patient should they grow.

Lipomas can also occur in body cavities and in the spinal canal (Mayhew & Brockman 2002).

Infiltrating lipomas should be removed with wide clean margins as otherwise they will inevitably recur (Weimaraners may develop multiple infiltrating lipomas). Diagnosis is based on histopathology and clinical appearance of local invasion. They do not metastasize but are locally aggressive and invasive. These tumours are often intimately associated with underlying muscle and a contrast-enhanced CT or MRI scan is required to fully assess the extent of the tumour (**Figure 18.5**). With complete excision the prognosis is good; however, if they recur, multiple surgeries are often required. The role of radiotherapy in preventing recurrence is generally unproven, but a small number of cases treated with fine-fractionated megavoltage radiation did well (McEntee & Thrall 2001).

Liposarcomas are the malignant variant and will be discussed with other soft tissue sarcomas separately (see Chapter 20).

Intermuscular lipomas are located in the caudal thigh (between semitendinosus and semimembranosus muscles) in dogs. They are benign and generally slow growing, but can cause lameness and neurological deficits with compression of the sciatic nerve once they reach a large enough size. Treatment is removal by careful blunt dissection (to avoid damage to sciatic nerve), with an excellent prognosis (Thomson et al 1999). Other locations include between the muscles of the chest wall and between the pectoral muscles of the forelimb.

Melanoma

Unlike humans, dogs and cats do not seem to develop malignant melanomas due to exposure to ionizing solar radiation. Tumours of melanocytes and melanoblasts are relatively common skin tumours in dogs. They are most common in older animals with darker coats. Melanomas can be found associated with haired skin, nail bed or oral cavity (see Chapter 13) and the biological behaviour of the tumour is correlated with location.

Cutaneous melanoma can be either benign or malignant. The benign form is often referred to as melanocytic nevus, and is well-defined, firm, dome-shaped, <2 cm in diameter and mobile. Malignant melanomas appear to grow rapidly and are

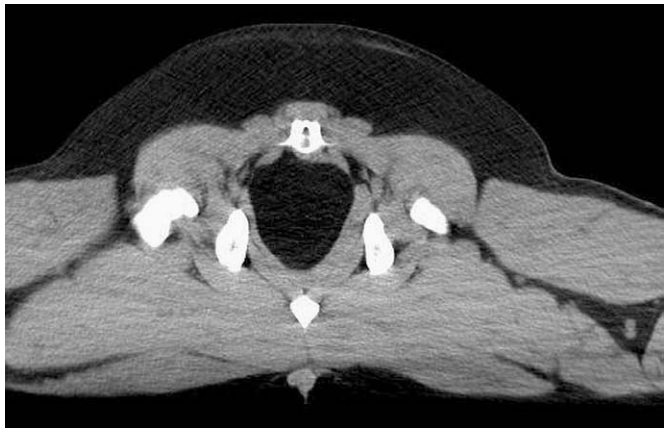


Figure 18.5 Contrast-enhanced CT scan of intrapelvic lipoma; dog presented for tenesmus.

often ulcerated (Vail & Withrow 2007). Over 85% of haired cutaneous forms are benign. Most oral and mucocutaneous (except eyelid) and 50% of nail bed (subungual) melanomas are malignant. Mitotic rate is highly predictive of the degree of malignancy and a mitotic rate of <3 per 10 high-power fields is strongly associated with benign behaviour (Aronsohn & Carpenter 1990, Bolon et al 1990, Bostock 1986). Poodles have a high percentage of malignant tumours. Additional analysis by flow cytometry has shown a correlation between DNA ploidy and malignancy (Bolon et al 1990).

Treatment is surgical excision, providing an excellent prognosis for benign tumours, whilst those with malignant properties have a 30–75% metastatic rate (Aronsohn & Carpenter 1990, Bolon et al 1990). For those patients where local excision cannot be guaranteed, radiotherapy should be considered to achieve complete local control. Radiation therapy can also be applied to dermal malignant melanoma where excision is not possible due to size or location, and can also be used to shrink a large tumour for follow-up surgery. Systemic chemotherapy for malignant melanoma in the dog has thus far not shown any significant benefit.

As with SCC, subungual melanomas deserve a special mention. Melanoma is the second most common neoplasm of the ungual region and, as with SCC, is often mistaken for paronychia. Digital radiographs should be taken in any patient with persistent paronychia but in the case of melanoma the majority of patients do not show digital lysis. Once a biopsy has confirmed melanoma, the regional lymph node should be evaluated and thoracic radiographs taken. Approximately 50% of these tumours will metastasize with a median survival time of 1 year (Marino et al 1995). The treatment of choice is digital amputation. If excision cannot be guaranteed, radiotherapy is advised to ensure long-term local control. The prognosis is guarded because of the high metastatic potential of these tumours. Systemic chemotherapy has not been shown to improve survival times in these patients. However, the availability of an anti-melanoma vaccine may improve survival times.

Cutaneous smooth muscle tumours

These arise from the erector pili muscles or smooth muscles of the dermal vasculature. They can recur after incomplete excision but metastasis has not been reported (Liu & Mikaelian 2003).

Tumours metastatic to skin

The most common tumour metastatic to the skin is HSA. For a full discussion of cutaneous HSA, see Chapter 20.

Other tumours with documented cutaneous metastases include anaplastic carcinomas and rarely sarcomas, e.g. osteosarcoma. Melanomas will also frequently metastasize to the skin. Cutaneous metastasis warrants a poor prognosis.

FELINE TUMOURS

In the cat the proportion of malignant tumours is greater than in the dog and therefore means that all feline 'lumps and bumps' should be investigated early.

Epithelial tumours

Basal cell tumours

These are the most common benign skin tumours seen in the cat (Vail & Withrow 2007). They are usually solitary, rounded and well circumscribed and may be pigmented. Surgical excision is the treatment of choice. Malignant basal cell carcinoma is rarely seen; however, as in the dog, it is locally invasive and if adequate excision is not possible, adjuvant radiotherapy should be considered (**Figure 18.6**).

Sebaceous gland tumours

These tumours are rare in the cat and the treatment of choice is surgical excision.

Sweat gland tumours

These tumours most often arise in the inguinal or axillary region. Presentation is variable with solitary nodules or a diffuse ulcerative plaque-like lesion. The majority of sweat gland tumours are malignant and wide surgical excision is the treatment of choice. The efficacy of chemotherapy has not been proven.

Ceruminous gland tumours

For a discussion of tumours of the feline ear canal, see Chapter 13.

Squamous cell carcinoma (SCC)

In the cat, SCC is most often seen in the lightly pigmented skin of the pinnae, nasal planum and eyelids, and is

Figure 18.6 Basal cell carcinoma in a cat.

usually preceded by solar keratitis. It can be either proliferative or erosive and approximately 30% of cats will have multiple lesions (Vail & Withrow 2007). A progression of disease can be seen over many months, with the disease often starting as superficial crusting (actinic keratitis) leading to carcinoma in situ and finally invasive SCC. Generally, SCC of facial skin in cats is locally invasive but late to metastasize.

A number of treatment options are available and the suitability of each treatment depends on the size, extent and multiplicity of lesions. In some cases treatment choice will also be made on the basis of cost, availability and cosmetic appearance. The list of treatments includes surgical excision (pinnectomy, nasal planectomy), external beam radiation, PDT, brachytherapy, cryotherapy, Strontium-90 therapy and intralesional chemotherapy. (For details of each modality, the reader is referred to the appropriate chapters.) These treatments are all most successful in managing small lesions (<5 cm), and for some modalities (e.g. PDT, strontium and cryotherapy) they are applicable only to superficial lesions. External beam radiation and surgery are applicable to both superficial and invasive lesions. Large, locally invasive lesions have a poorer prognosis, due to recurrent/residual local tumour. Palpation (+ biopsy if enlarged) of regional lymph nodes should be performed. Thoracic radiography may be indicated for cats with severe or recurrent disease due to the possibility of metastases.

A variation of SCC in cats is referred to as multicentric SCC in situ (MSCCIS), Bowen's disease or bowenoid carcinoma in situ (Baer & Helton 1993, Miller et al 1992, Rees & Goldschmidt 1998). MSCCIS is found in haired and pigmented skin, and is not associated with UV light/sun exposure, feline leukaemia virus (FeLV) or feline immunodeficiency virus (FIV). An association with papillomavirus has been reported. Lesions are confined to the epithelium, and are crusty, haemorrhagic and painful. Treatment is surgical excision where possible. Local recurrence has not been reported when excision is possible; however, other lesions may develop in other locations. Other modalities that may be beneficial in the treatment of small lesions are Strontium-90 or PDT (Vail & Withrow 2007).

Feline sarcoid (dermal fibropapillomas) are usually solitary (rarely multiple), firm, alopecic and often focally ulcerated masses. They are most common in young cats (median 4 years) on the head, neck or digits. An association with papillomavirus has been documented with this disease in cats. Local recurrence after surgical excision is 30–50% but metastasis has not been documented (Vail & Withrow 2007).

Round cell tumours

Mast cell tumour (MCT)

For a detailed discussion of mast cell tumour, see Chapter 19.

Cutaneous lymphomas

For a detailed discussion of cutaneous lymphomas, see Chapter 22.

Histiocytic tumours

Benign histiocytomas have not been recognized in the cat but histiocytic disease syndromes have been identified.

Feline progressive histiocytosis

Cats may have either a solitary nodule or a number of plaques, papules or nodules (Affolter & Moore 2006). They are typically alopecic, firm and non-painful, and eventually they may ulcerate. Lesions are typically located on the head, lower extremities or trunk. Generally, the nodules progress in size and may coalesce. In some cases organs beyond the skin are involved to include the lymph nodes, liver, lung, spleen and kidneys. No successful treatment has been recognized although the authors have had a transient response to radiotherapy for isolated lesions on the face.

Histiocytic sarcoma (HS)

The clinical presentation of HS in the cat is essentially the same as in the dog, but the incidence is markedly reduced. Treatment options are the same and the prognosis should be considered guarded to poor, depending on organ involvement and disease progression.

Malignant fibrous histiocytoma

For a discussion of this soft tissue sarcoma, see Chapter 20.

Tumours of mesenchymal origin

The most common neoplasm of mesenchymal origin seen in the cat is injection-associated sarcoma and this, in addition to the other soft tissue sarcomas seen in cats, will be discussed in Chapter 20.

Melanoma

In the cat, melanoma can also be benign or malignant. In general, ocular melanoma (see Chapter 25) is more behaviourally malignant than oral melanoma (see Chapter 13), and dermal forms are more likely to have a benign course. Cutaneous melanoma occurs more often on peripheral sites such as head, tail and limbs. Histological assessment is not predictive of outcome (Luna et al 2000). The usual presentation is a slow-growing nodule that may appear benign; however, they can show local recurrence, with spread to regional lymph nodes and wide metastasis.

Treatment is surgical excision, providing an excellent prognosis for benign tumours. Those with malignant properties have a guarded prognosis. Radiation therapy may also be an alternative to surgery for dermal malignant melanoma where excision is not possible. No benefit from systemic chemotherapy has been proven.

Tumours metastatic to skin

In the cat, primary nail bed tumours are rare, but are a location for metastatic carcinomas – for example, bronchiolar adenocarcinoma, pulmonary SCC and cutaneous SCC may metastasize to the digits. In cases where metastasis has occurred to the digits, the prognosis is poor.

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Mast cell tumours

Perhaps the most difficult of all the tumours we deal with in veterinary medicine is the mast cell tumour (MCT). Because it is a common tumour, every veterinary surgeon at some point in their career will be pulling their hair out trying to decide on the correct course of action for an individual patient. This is because not only can MCT present with many variations in appearance (the great pretender), the management of the tumour itself and its biological behaviour can be difficult to predict.

CANINE MAST CELL TUMOURS

Incidence

MCT are the most common cutaneous tumours seen in the dog (16–21%) (Bostock 1986, Rothwell et al 1987). They affect mostly older dogs with a mean age of 9 years, but the age range is considerable (3 weeks to 19 years) (Davis et al 1992, Patnaik et al 1984). Breeds with bulldog ancestry are over-represented – Boxers, Bull Mastiffs, Boston Terriers. Other breeds with a predisposition to develop MCT include Labrador Retrievers, Golden Retrievers, Shar Peis, Weimaraners, Schnauzers and Beagles. In the author's (TB's) experience in Australia, Staffordshire Bull Terriers are also at high risk and often develop high-grade tumours. No sex predilection has been documented.

Aetiology

Aetiology is unknown, but genetic alterations in expression of c-*kit* (a stem cell factor membrane receptor, capable of triggering cell growth and normally expressed on haemopoietic and mast cells) have been shown in some canine MCT (Dank et al 2002, Downing et al 2002, Jones et al 2004, Reguera et al 2002, Riva et al 2005, Zemke et al 2002). It has also been proven that canine MCT cells express c-*kit* (London et al 1996), and dysregulated expression of c-*kit* may contribute to MCT development (Turin et al 2006).

Clinical signs

In the majority of cases clinical signs are associated with the primary tumour; rarely, systemic signs will occur as the initial complaint.

The clinical appearance of MCT is extremely varied, so any skin lump could be an MCT, regardless of its appearance (**Figure 19.1**). Fine needle aspirate (FNA) cytology and/or histopathology are needed to confirm the presence of an MCT. The majority of dogs present with solitary lesions, but 11–14% have multiple tumours (**Figure 19.2**) (Mullins et al 2006, Tams & Macy 1981, Van Pelt et al 1986).

A long, stable history is more consistent with lower-grade MCT. High-grade MCT tend to be rapidly growing and the surrounding tissues may be inflamed and oedematous; occasionally small satellite nodules are present.

The dermis and subcutaneous tissues are frequent MCT sites, with up to 50–60% of cases on the trunk, 25% on the limbs and less frequently on the head and neck. Other unusual locations include conjunctiva (**Figure 19.3**), salivary gland, nasopharynx, larynx and oral cavity (Bostock 1973, Iwata et al 2000, Rothwell et al 1987).

Darier's sign results from the mechanical manipulation of MCT, causing degranulation with resultant erythema and wheal formation in surrounding tissues.

Gastrointestinal problems, e.g. vomiting (possibly with blood), anorexia, melaena and abdominal pain, may result from MCT degranulation.

Pleural and peritoneal effusions in dogs with disseminated mastocytosis may contain neoplastic mast cells.

Diagnostic work-up

Clinical examination

The clinician should be aware that tumour location affects tumour behaviour and prognosis (see 'Prognostic factors' below). A thorough search of the animal for multiple cutaneous masses should be performed and any new lump found should undergo FNA cytology. If multiple cutaneous MCT are found, the approach to treatment is often different from that for a single MCT.

Initial diagnosis is via FNA cytology

The majority of MCT can be identified on FNA. They appear as small-to-medium round cells, usually abundant and with uniform cytoplasmic granules that stain purple-red (metachromatically) (**Figure 19.4**). However, grade cannot be determined by cytology and it is important to remember that not all MCT stain with Romanovsky-type stains, giving them an epithelial or macrophage-like appearance on the slide. In such cases, histology and possibly immunohistochemistry are required for diagnosis. In some cases FNA of an MCT will only yield blood.

Evaluation of the primary tumour

Prior to surgery it is important to assess the extent of the local tumour. In some cases this can be very difficult when the tumour is fluctuant and does not appear to have defined

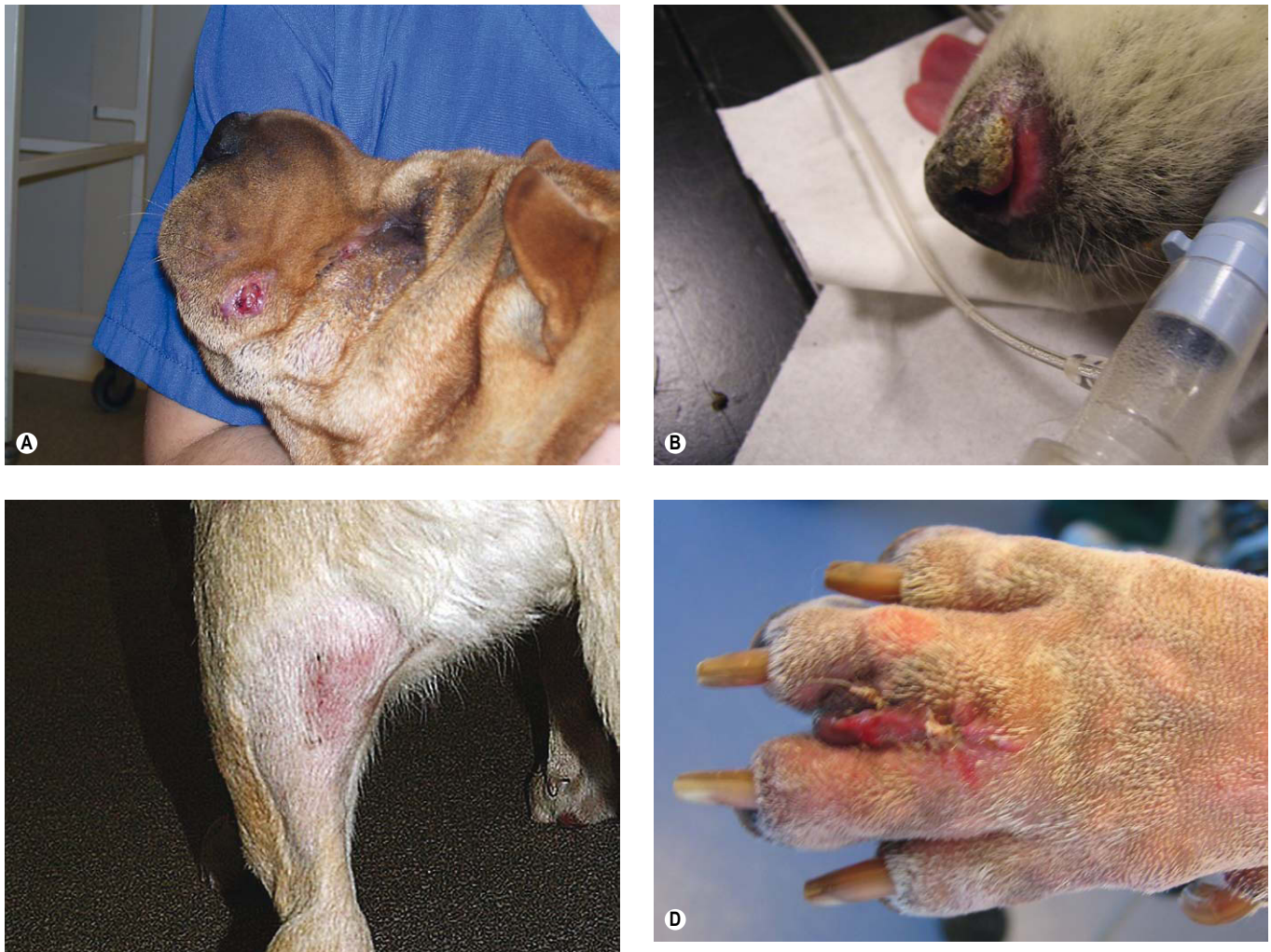

Figure 19.1 The various manifestations of mast cell tumour (MCT). (**A**) High-grade MCT on the face of a Shar Pei. (**B**) MCT on nose of a German Shepherd. (**C**) Fluctuant MCT on the tarsus of a Labrador. (**D**) MCT in the interdigital space.

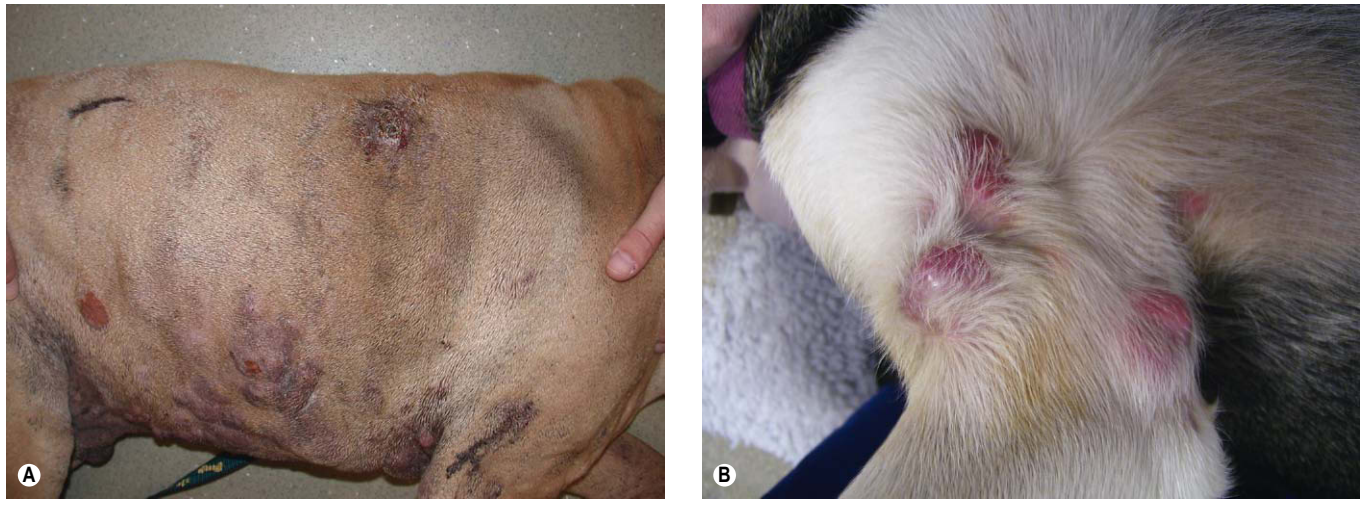

Figure 19.2 (**A, B**) Dogs with multiple cutaneous mast cell tumours.

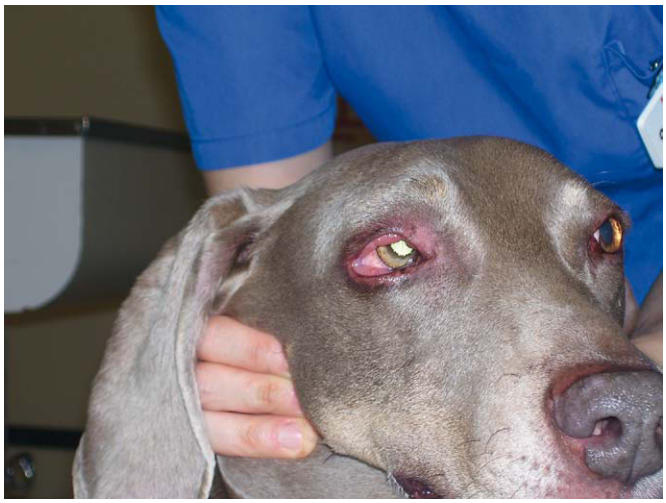

Figure 19.3 Weimaraner with conjunctival mast cell tumour.

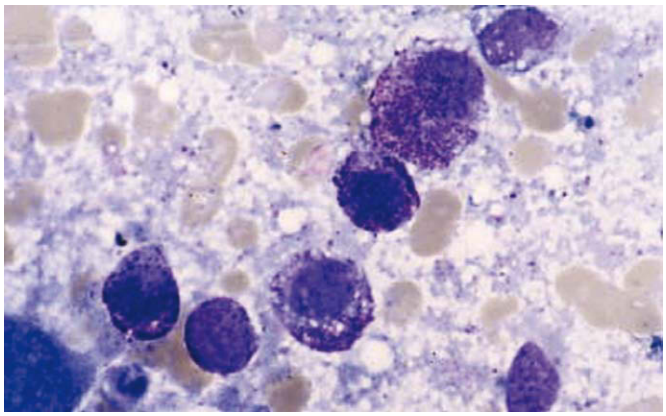

Figure 19.4 Typical cytological appearance of mast cell tumour.

margins. It can also be difficult in those tumours that constantly wax and wane. Whenever an MCT undergoes a local inflammatory response resulting in a transient increase in size, it must be assumed that tumour cells extend into the affected area. Therefore, the presurgical use of steroids to reduce tumour size results in underestimation of the size of the tumour and potentially incomplete resection. Shrinkage of a tumour before surgery with radiotherapy, however, is completely different in that the edges have been truly sterilized.

The extent of the tumour can be estimated by physical examination, radiographs, ultrasound or computed tomography (CT) scan. Interestingly, in one study, dogs with cutaneous MCT had the extent of the margin upgraded in 19% of cases using ultrasound and 65% of cases using CT (Hahn et al 1990). This is important for planning surgery and radiotherapy. What additional tests are required to establish the extent of the tumour depends on its location and whether a wide excision will be simple or difficult.

Staging

What is the importance of staging?

The more information that is obtained, the more accurate the predictions as to prognosis. In terms of treatment this means that the most appropriate course of treatment can be determined. It is also important to understand the relevance of normal responses in the body that may account for the presence of mast cells. Interestingly, MCT do not metastasize or originate in the lungs.

Additional presurgical diagnostics include the following.

- Evaluation of the regional lymph node (RLN): If the node can be palpated, FNA should be undertaken (even if normal in size). When interpreting a cytological report in which a small number of mast cells are found it is important to remember that mast cells are normal components of lymph nodes. If the lymph node is potentially positive for regional spread, excisional biopsy at the time of surgery is indicated. It is the morphological features of the mast cells in addition to their distribution throughout the node that define early metastasis. Obviously, if the node is significantly enlarged and full of mast cells, cytology is sufficient for diagnosing metastatic MCT.
- Radiographs are of less value in patients with MCT than any other neoplastic process and can usually be eliminated from the work-up of a young patient. In older dogs it is advisable to take thoracic radiographs to ensure that there are no other problems, but it is important to remember that the lung is not a metastatic site for MCT. It is also important to understand the drainage pattern of the lymph nodes to ensure that the sentinel node is checked. Occasionally, intrathoracic nodes will be enlarged in patients with MCT of the forelimbs, and sub-iliac lymph nodes in patients with hindlimb involvement; the sentinel node for aural MCT is the superficial cervical (or pre-scapular) node.
- Abdominal ultrasound to evaluate the liver and spleen is a more valuable diagnostic tool than abdominal radiographs. Abnormalities in these organs (usually hepatosplenomegaly) and a 'Swiss cheese' appearance should be evaluated by FNA. The major non-neoplastic differential diagnosis for this 'punched-out' appearance in the spleen is splenitis. Disseminated MCT in either the liver or spleen can be diagnosed on FNA; however, a small number of mast cells should be viewed cautiously as these cells can normally be present in these locations, especially if they are morphologically normal.
- Buffy coat analysis is currently rarely of value in the work-up of the patient with MCT unless the patient is physically unwell, e.g. vomiting, diarrhoea, etc., or has very aggressive MCT affecting major organ systems.
- For the same reason as in buffy coat analysis, bone marrow aspirates are rarely performed. A bone marrow aspirate is more accurate than buffy coat analysis. Patients with a positive bone marrow have a poor prognosis.
- Incisional biopsies can be carried out to establish grade prior to surgery.

What should be the extent of staging prior to surgery?

One approach is this:

- If the tumour is excisable with wide margins, and there are no negative prognostic factors, further staging is not

needed, and regular postoperative rechecks for local recurrence and palpable RLN enlargement should be sufficient. Further staging could then be performed postoperatively for grade II or III mast cell tumours.

- However, if the MCT is not amenable to wide excision (e.g. distal extremity), or if negative prognostic factors exist in the history or physical examination (see above), ancillary diagnostic tests to stage disease are performed prior to definitive treatment to better advise clients of probable outcomes and to help plan the type and extent of definitive therapy.

Prognostic factors

Known prognostic indicators are as follows.

Histological grade

This is strongly predictive of outcome (Thamm et al 2006). In spite of some 'greyness' in defining histological grade, it is highly predictive for overall survival time, providing appropriate therapy is given from the beginning. The vast majority of dogs with well-differentiated tumours (80–90%) and 60–75% of moderately differentiated tumours experience long-term survival following surgical excision ± radiotherapy. Dogs with undifferentiated (high-grade) tumours treated surgically frequently die of their disease within 12 months due to local recurrence or metastasis.

Individual histological criteria such as invasiveness and the number of mitotic figures were prognostic in one study. These parameters may be more reliable than the Patnaik grading system, which is influenced by more subjective observations such as tumour heterogeneity, cellular differentiation and nuclear morphology (Preziosi et al 2007).

Clinical stage

In combination with histological grade, stage is predictive of long-term prognosis (see Table 19.1). Patients with stage 0-I disease confined to the skin without local lymph node involvement or distant metastasis have a better prognosis than patients with stage III–IV disease. At least one study has suggested that there is no difference in outcome between patients with a single MCT and those with multiple cutaneous MCT (Mullins et al 2006, Simoes et al 1994, Thamm et al 2006).

Location

In general, our ability to recognize MCT earlier and combine better surgical approaches with radiotherapy has resulted in overall better survival times for patients with MCT. However, certain locations may still warrant a more guarded long-term prognosis; in particular, aural (early metastasis to regional lymph nodes), subungual, perianal, oral and other mucocutaneous sites are associated with more undifferentiated tumours and a poorer prognosis, with metastasis earlier in the course of their disease (Cahalane et al 2004, Sfiligoi et al 2005, Thamm et al 2006). Any MCT at a mucocutaneous site is considered grade III disease (due to metastatic potential) no matter what grading they are given by the pathologist. Visceral disease carries a grave prognosis (O'Keefe 1990, Ozaki et al 2002).

Growth rate

This is determined by tumour volume/number of weeks the tumour was present. Low-grade MCT tend to have a long, stable history. Some MCT will remain sessile for weeks, months or even years before entering a phase of rapid growth; the biological trigger is unknown.

Any growing MCT should be removed immediately, as should any 'quiescent' MCT located in an area where growth would compromise surgical margins, e.g. distal extremity or face. Rapid growth is a negative prognostic indicator and the faster an MCT is growing, the sooner it should be addressed. Best practice is to diagnose and treat as early as possible. A 'wait and see' approach is potentially detrimental to the patient.

Table 19.1 Clinical staging for canine mast cell tumours (MCT)

Stage	Characteristics
0	One MCT incompletely excised from dermis without lymph node involvement: a) without systemic signs b) with systemic signs
I	One MCT confined to the dermis, without lymph node involvement: a) without systemic signs b) with systemic signs
II	One MCT confined to the dermis with lymph node involvement: a) without systemic signs b) with systemic signs
III*	Large infiltrating MCT with or without lymph node involvement: a) without systemic signs b) with systemic signs
IV	Any tumour with distant metastasis, including blood or bone marrow involvement

*The WHO staging system lists multiple dermal MCT as clinical stage III disease. However, multiple MCT confined to the dermis have not been shown to have a worse prognosis, and are not analogous to a large, infiltrating MCT.

Systemic signs

Vomiting, melaena, anorexia, or widespread erythema and oedema due to massive mast cell degranulation are more often associated with large cutaneous MCT or disseminated disease (Mullins et al 2006, O'Keefe 1990, Pollack et al 1991). In 16 cases of visceral MCT, the median survival time (MST) was 90 days and all dogs died of MCT (O'Keefe 1990).

Recurrence

Recurrence following surgical excision is thought to carry a more guarded prognosis (Thamm et al 2006).

Breed

Boxers usually have well-differentiated tumours and therefore a better prognosis (Bostock 1986). Other breeds that have a predisposition to develop more biologically aggressive MCT include Bernese Mountain Dogs (BMD), Shar Pei and Bull Mastiff. Multiple cutaneous MCT are seen most frequently in Boxers, Golden Retrievers, Labrador Retrievers and Weimaraners.

Additional prognostic factors

In an attempt to better understand prognosis for patients with MCT, new indicators are constantly been evaluated.

The first of these was evaluation of argyrophilic nuclear organizer regions (AgNORs). AgNORs are an indirect measure of cell proliferation and require silver colloid staining of paraffin-embedded sections. The number of AgNORs has been correlated with histological grade and postsurgical outcome. The higher the count, the poorer the prognosis tends to be (Bostock et al 1989, Simoes et al 1994). The main problem with AgNORs is subjectivity; it is very operator dependent and not widely available.

Proliferating cell nuclear antigen (PCNA) is a 36 kD acidic non-histone protein required for DNA synthesis and is an immunochemical test that again is an indirect assessment of tumour cell proliferation (Abadie et al 1999, Simoes et al 1994).

Other cellular proliferation indices include Ki-67 and this, in combination with AgNORs and PCNA-positive nuclei, may indicate the likelihood of MCT recurrence after incomplete excision (Séguin et al 2006). BrdU LI (bromodeoxyuridine) is another marker of cellular proliferation correlated with tumour grade (Sakai et al 2002).

Intratumoral microvessel density correlates to invasiveness, mitotic rate and prognosis (Preziosi et al 2004). Microvessel density/angiogenesis was significantly higher in high-grade MCT compared to intermediate and low-grade MCT (Ranieri et al 2003).

Other markers currently being evaluated include c-*kit* mutation and high-grade tumours (Zemke et al 2002), Mdm2 expression (an immunohistochemical marker that plays a crucial role in mast cell tumorigenesis and is consistent with histological grade) (Wu et al 2006), and aberrant CD117 immunoexpression patterns and higher histological grade (Gil da Costa et al 2007).

Treatment

This depends on presence or absence of negative prognostic factors, and on the clinical stage of disease. Surgical excision with clean margins and marginal excision with adjuvant radiation therapy are the most successful treatment options to date.

Surgery

For tumours localized to the skin or subcutaneous tissues in areas amenable to wide excision, surgery is the treatment of choice.

The surgeon should include a 3 cm margin of surrounding normal tissue. However, margins of 2 cm may be sufficient for low- and intermediate-grade MCT (Simpson et al 2004) (**Figure 19.5**). Wide margins are deep as well as lateral, and for a deep margin a fascial plane is required to ensure adequate excision (see Chapter 5). Histological assessment of margins is important. If planned curative surgery has not been achieved, then further local therapy may be warranted. This may entail a second excision with additional wide margins or adjuvant radiation therapy depending on MCT location. Not all incompletely resected MCT will recur, especially if low–intermediate grade and the possibility of normal mast cells at tissue margins may cause some confusion (Séguin et al 2006). However, if the resection is incomplete and recurrence would be difficult to deal with (distal extremity or face), adjuvant therapy is indicated.

Wide margins to ensure adequate excision of MCT mean that in many cases flaps are required (**Figure 19.6**). It is important that before a flap is attempted the surgeon is entirely confident that this will result in complete excision. If not, it is better for the patient to do a marginal excision and refer for radiotherapy. There is nothing worse than putting a patient through the long process of recovering from extensive surgery and then not having a margin, because at that point the radiation oncologist has to assume potential recurrence in any region of the flap. It also makes the whole process more expensive for the client than it needed to be.

For many patients the long-term prognosis with surgery alone is good. Patnaik et al (1984), in a large retrospective study, showed that 1550 days after surgery 93% of dogs with well-differentiated MCT were alive, compared with 44% with intermediate-grade tumours and only 6% with poorly differentiated tumours. A number of studies since then have come to similar conclusions concerning prognosis (Murphy et al 2004, Séguin et al 2006, Sfiligoi et al 2005).

MCT often arise in areas where it is not possible to achieve adequate surgical margins, e.g. the head and distal extremities. In the case of a MCT on a distal extremity, amputation of the leg is an option and in some cases can be the treatment of

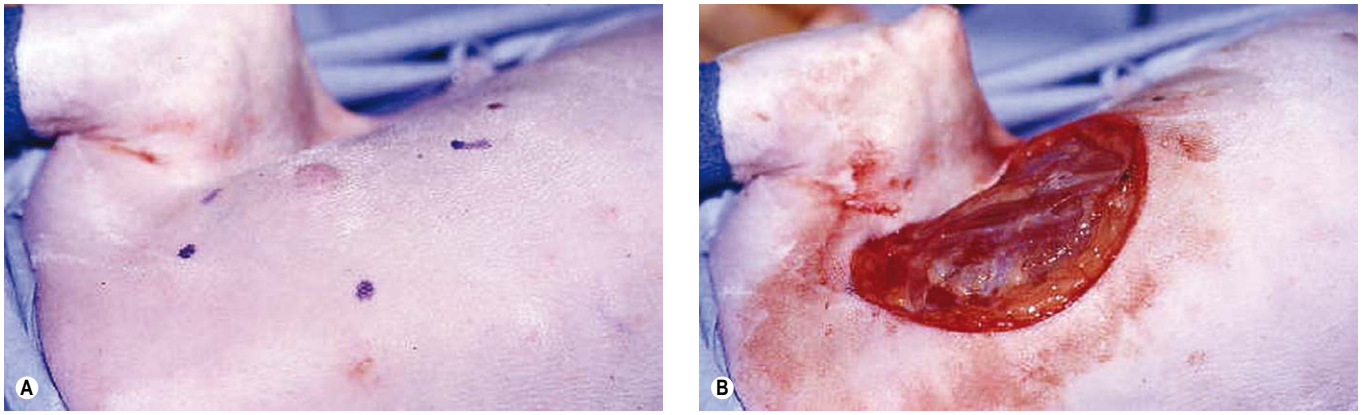

Figure 19.5 (**A, B**) Planning surgery in a dog with a mast cell tumour on the ventral abdomen.

Figure 19.6 (**A, B**) Lateral geniculate flap in a dog with a mast cell tumour.

choice, especially if the tumour has extended 360 degrees around either the carpus or the tarsus. Usually, however, amputation is seen as a salvage procedure and in most cases the goal is to preserve the limb.

Regardless of local therapy, dogs with low–intermediate grade MCT should be re-evaluated regularly for local recurrence and regional spread.

For tumours where adequate margins are not achievable, e.g. tumours of the extremities, ensure that the grade is known via incisional biopsy before treatment.

Low–intermediate grade tumours

- Treatment of choice is marginal resection and radiation. Clinical stage 0 disease and follow-up with radiation produced 2-year control rates of 85–95% for stage 0 tumours of low or intermediate grade (Al-Sarraf et al 1996, Frimberger et al 1997, LaDue et al 1998, Turrel et al 1988). Prophylactic radiation of cytologically negative lymph nodes can be performed but definitive evidence for survival advantage is lacking (Poirier et al 2006).
- Limb amputation: wide margins but least functional outcome.
- External beam radiation alone: 40–50 Gy gives 1-year control of 50% (Turrel et al 1988). Coarse-fraction radiation (3–4 weekly, 8–10 Gy) gives local responses lasting 1 year or longer.
- Marginal resection and chemotherapy (alternate choice if radiation is not available) (Thamm et al 2006).

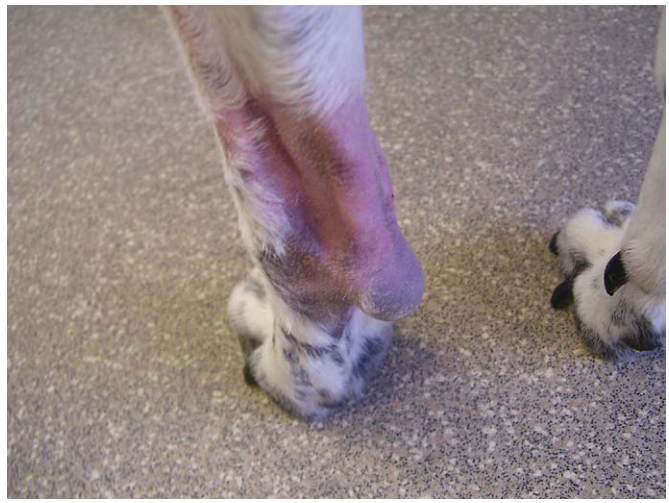

Figure 19.7 The typical radiotherapy patient with an incompletely resected mast cell tumour.

For patients with positive lymph nodes (determined on histopathology) adjuvant chemotherapy is advisable and the authors recommend three cycles of CCNU (lomustine) at intervals of 3 weeks with follow-up rechecks for lymph node and liver/spleen assessment at 3-monthly intervals for 1 year. In many patients with early metastasis to the lymph node, surgical excision plus chemotherapy may be sufficient to prevent further spread, so although these patients have a more guarded prognosis, regional involvement does not preclude definitive treatment for the primary tumour.

Poorly differentiated tumours

For any patient with distant metastasis or poorly differentiated tumours the overall prognosis is poor and treatment options may be palliative rather than definitive.

- The treatment of choice for poorly differentiated tumours without obvious metastases is surgery/radiotherapy for local control and chemotherapy for metastatic disease.
- For patients with obvious metastatic spread the value of extensive surgery is questionable except in cases when a lack of treatment for local disease would reduce quality of life for the patient. This can be a difficult decision for both the veterinary professional and the client, requiring that the client be informed of all the options.
- Palliative treatment would include chemotherapy or prednisolone (see below).

Radiotherapy

In veterinary medicine the most frequent application of radiotherapy is in the control of incompletely resected MCT. Radiotherapy should be considered in all patients where an MCT has been incompletely resected and where no further surgery can be carried out to obtain surgical margins. This means that the majority of patients eligible for radiotherapy have had MCT on the head/muzzle region or a distal extremity (**Figure 19.7**).

The decision as to the value of radiotherapy in an individual patient depends on the experience of the radiation oncologist. The rule of thumb used by the authors is that any

fast-growing/aggressive MCT in an area of the body that would be difficult to re-excise should it regrow should receive radiation. Any MCT that has shown invasion onto tendons etc. should also be irradiated, irrespective of grade. MCT that may be best monitored are those of lower grade, less invasive or in areas that should there be recurrence, good options for further treatment are available.

Age and breed can also influence treatment decisions. The younger the patient, the better it is to avoid radiotherapy for MCT, if possible, because of the potential for long-term side effects of treatment (see Chapter 7).

A number of treatment protocols are available in the literature but all give good long-term control for stage 0 tumours of low to intermediate grade (median 2-year control rates of 85–90%). Radiotherapy is equally successful in local control of high-grade MCT but unfortunately these patients fail early due to metastatic disease.

Radiotherapy can also be used to shrink tumours before surgery and actually sterilizes the margins so that these are not underestimated at the time of surgical excision.

Radiotherapy can be used as the sole treatment in the management of MCT. In this scenario, it should be considered palliative therapy and is most often applied to MCT located on the muzzle not amenable to surgery or the client declines surgery due to the potential cosmetic appearance, e.g. MCT of the distal extremities that are not amenable to surgery and the client declines amputation. The major concern in irradiating bulky MCT is mast cell degranulation and the resulting consequences of acute hyperhistaminaemia.

Large MCT can be considered for radiotherapy to shrink them down to improve quality of life. However, the potential for complications, as above, is high, and such patients require hospitalization after treatment.

Chemotherapy

The role of chemotherapy remains an area of discussion in veterinary medicine. The primary treatment modalities are undoubtedly surgery and radiotherapy. However, in patients with metastatic disease (**Figure 19.8**) or multiple cutaneous MCT, surgery and radiotherapy may not be appropriate. In general, for multiple cutaneous MCT, multiple marginal excisions are combined with adjuvant chemotherapy.

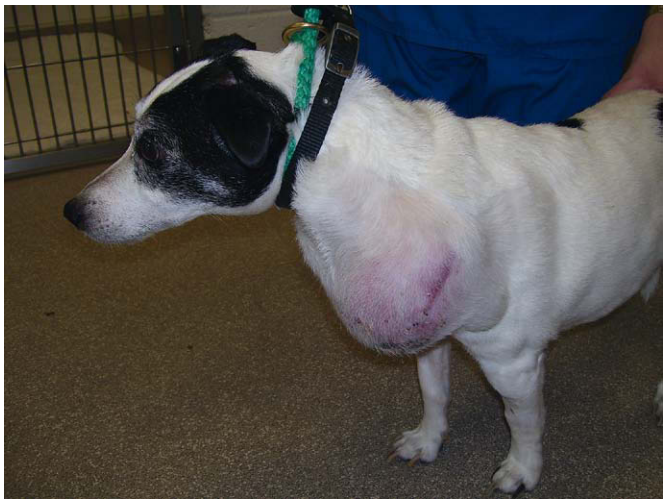

Figure 19.8 Metastatic high-grade mast cell tumour.

Chemotherapy can also be used as a sole agent for palliation of patients with multiple MCT. A number of drugs have been tried in the management of canine MCT, including prednisolone (McCaw et al 1994), L-asparaginase, doxorubicin, vincristine (McCaw et al 1997), cyclophosphamide (Elmslie 1997), chlorambucil, hydroxyurea (Gerritsen et al 1998), vinblastine (Thamm et al 1999) and lomustine (CCNU) (Rassnick et al 1999), either alone or in combination.

Prednisolone

Glucocorticoids have a number of effects on MCT.

- They inhibit production of growth factors and cytokines on which new cells depend.
- They inhibit the normal pattern of granule formation.
- They are anti-inflammatory and anti-pruritic.

In one study, 25 dogs with MCT were given prednisolone at 1 mg/kg for 28 days; the response rate was 20% (McCaw et al 1994). The primary effect of prednisolone is to decrease the growth and reproductive rate of mast cells. Poorly differentiated mast cells have fewer glucocorticoid receptors and are naturally more resistant to steroids.

Prednisolone is not recommended as sole treatment for MCT unless all other treatments have been declined. It is valuable in the management of paraneoplastic syndromes (PNS) associated with MCT, to reduce inflammation during radiotherapy and is often included in chemotherapy protocols for the management of metastatic disease. In the latter scenario the authors recommend a 6-week reducing dose of prednisolone.

Vinblastine

Vinblastine has shown efficacy in the management of MCT (Thamm et al 1999). The usual protocol consists of weekly for four treatments (2 mg/m^2) then every other week for an additional four treatments. Prednisolone is usually included in the protocol (concurrently 1 mg/kg p.o. sid for 2 weeks, then 0.5 mg/kg, then stopped once vinblastine is stopped). Patients receiving prednisolone/vinblastine for high-grade MCT had MSTs of 331 days, with 45% of patients available for evaluation alive at 1 and 2 years. This shows an improvement in survival times over historical cases treated with surgery alone (Thamm et al 1999).

CCNU (Lomustine)

CCNU and vinblastine are the chemotherapeutic agents of choice in the management of both metastatic MCT and multiple cutaneous MCT. They can be used singly or combined depending on the extent and aggressiveness of the disease. In one study, a 42% response rate to CCNU was demonstrated (Rassnick et al 1999). The ideal protocol has not yet been developed and the management of patients with multiple cutaneous MCT is different from patients with one MCT that has metastasized. Also, the response of metastatic MCT depends on grade, as patients with intermediate-grade metastatic MCT usually have a more prolonged response than patients with high-grade MCT.

In the authors' experience, single-agent CCNU (60 mg/m^2) every 3 weeks for three treatments is effective in patients with regional metastasis from intermediate-grade MCT. In patients with poorly differentiated MCT, alternating CCNU and

Table 19.2 Response rate of canine mast cell tumour to various chemotherapeutic drugs

Drug	Single or combination	Number of dogs	%CR	%PR	%ORR	Median response duration
Prednisolone	Single	25	4	16	20	NR
Vincristine	Single	27	0	7	7	NR
Lomustine	Single	21	6	38	44	79 days
Prednisolone/vinblastine	Combination	41	33	13	47	154 days
Prednisolone/vinblastine/cyclophosphamide	Combination	21	0	78	78	NR
COP-HU	Combination	17	23	35	59	53

%CR, complete response; %PR, partial response; %ORR, objective response rate; NR, not reported; COP-HU, cyclophosphamide, vincristine, prednisolone, hydroxyurea.

vinblastine is advised at intervals of 2–3 weeks. In patients with multiple cutaneous MCT CCNU is also beneficial. However, it must be remembered that these are individual tumours so the response rate can vary even in the same patient. Table 19.2 compares published protocols; however, care is required in interpreting this comparison as some are evaluating the response rate of a single drug and others are combinations of drugs.

Paraneoplastic syndromes (PNS) and MCT

A major problem in the management of canine MCT is PNS associated with the release of vasoactive substances, either when the tumour is handled at surgery or when bulky tumours respond to either radiotherapy or chemotherapy.

PNS associated with MCT

- Local ulceration and swelling, seen as fluctuations in size and a sentinel sign of MCT, are due to local oedema and inflammation caused by the release of histamine and proteolytic enzymes. Darier's sign can be seen with the manipulation of MCT, resulting in degranulation and subsequent erythema and wheal formation in surrounding tissues (Tams & Macy 1981).
- Delayed wound healing at the site of removal is thought to be due to various substances released by the tumour. Histamine may bind to H_1 and H_2 receptors on macrophages resulting in the possible release of a fibroblastic suppressor factor that may decrease fibroplasia and delay wound healing (Kenyon et al 1983).
- Coagulation abnormalities: Prolonged bleeding times are frequently reported but this is rarely a clinical problem. The release of heparin causes local bleeding; however, malignant mast cells have reduced levels compared to normal mast cells. While clinical evidence of haemorrhage is not typically associated with this phenomenon, localized haemorrhage at the time of surgery due to degranulation following tumour manipulation can be a serious complication, even in the presence of a normal coagulation profile. Protamine sulphate, a heparin antagonist, may be used in cases of intraoperative haemorrhage.
- Hypotensive shock: Perioperative degranulation of MCT and subsequent release of histamine and other vasoactive substances may also result in rapid peripheral vasodilation and potentially life-threatening hypotensive events. Prostaglandins in the D series secreted by tumour cells may mediate the hypotensive effects observed in humans with MCT.
- Gastrointestinal ulceration may be more common than is seen clinically because examination of necropsy specimens showed ulceration in between 35 and 83% of cases examined (Fox et al 1990, Howard et al 1969), but only a small number of patients present with signs consistent with gastroduodenal ulceration. The mechanism is that high levels of histamine released by mast cells act on parietal cells via H_2 receptors, resulting in increased HCl acid secretion. Plasma histamine increases in dogs with MCT and these dogs also have decreased plasma gastrin, which is normally released by antral G-cells in response to increasing acid concentration, acting as a negative feedback loop. Hyperhistaminaemia can be measured by evaluation of plasma gastrin using the relationship that plasma gastrin is inversely proportional to plasma histamine. However, the degree of hyperhistaminaemia could not be predicted by clinical or histological stage of tumour size. The determination of urine histamine levels can be used as a diagnostic tool. Increased gastric acid secretion with vascular damage is likely to be the cause of gastric ulceration. Histamine also damages vascular endothelium, leading to intravascular thrombosis and ischaemic necrosis.

Treatment of syndromes associated with MCT

Ancillary therapy for systemic effects of MCT degranulation is sometimes recommended, e.g. blocking all or some of the effects of histamine release via the H_1 blocker diphenhydramine (2–4 mg/kg p.o. bid) and the H_2 blockers cimetidine (4 mg/kg p.o. tid) or ranitidine (2 mg/kg bid). Omeprazole (0.5–1 mg/kg sid) is more potent than cimetidine and has a longer duration of action.

In cases where there is active evidence of gastrointestinal ulceration, the addition of sucralfate (0.5–1.0 g p.o. tid) and occasionally misoprostol (3 g/kg p.o. tid) is recommended.

Usually used only if:

- systemic signs are present
- tumour is likely to be entered or manipulated at surgery (cytoreductive)
- gross disease will remain and degranulation is likely to occur in situ (e.g. radiotherapy, corticosteroid therapy or chemotherapy for tumours that are not cytoreduced)

but not usually used if no gross disease remains and minimal tumour manipulation has occurred.

Alternative local therapies

None is as researched, clinically effective or practical as surgery, radiotherapy or surgery plus radiotherapy:

- hyperthermia and radiotherapy
- intralesional brachytherapy
- photodynamic therapy
- intralesional corticosteroids
- cryotherapy.

Intralesional deionized water has not proven to be beneficial. In fact, a poorer outcome was found for treatment with surgery and deionized water (27 dogs), compared to dogs treated with surgery alone (28 dogs) (Jaffe et al 2000).

Adjuvant electrochemotherapy (intralesional bleomycin followed by the application of trains of biphasic pulses) in 28 dogs gave an overall response rate of 85%, and a median estimated time to recurrence of about 53 ± 6.5 months (Spugnini et al 2006).

Non-cutaneous MCT

Intestinal MCT in the dog is rare and is not related to the cutaneous forms. The treatment of choice is surgical excision with wide margins, and in the one case the author (SN) has seen, the dog lived for 18 months after surgery with no sign of recurrence or metastasis. However, in a series of 39 dogs with primary MCT of the gastrointestinal tract, vomiting/diarrhoea/melaena were presenting signs, with 40% alive 30 days after admission and less than 10% alive after 6 months (Ozaki et al 2002). One case report of a Boxer with an unresectable intestinal MCT and widespread lymph node metastasis showed a partial remission for 7 months when treated with CCNU and prednisolone, before euthanasia due to chemotherapy-induced sepsis (Baldi et al 2006).

Visceral MCT

In patients with visceral disease, buffy coat smears were positive for mast cells in 37% of cases, and 56% of bone marrow aspirates revealed mast cell dissemination (O'Keefe 1990). Visceral MCT showed peripheral eosinophilia in 13% and basophilia in 31% of cases. It is important to remember that mast cells are also found in normal tissue: approximately 24% of normal lymph node aspirates (1–16/slide, mean 6.4/slide) (Bookbinder et al 1992); and 2 of 51 bone marrow aspirates (McManus 1999). In addition, allergic disease or other inflammatory disease may also produce peripheral mastocytaemia (1–90/ l), e.g. parvovirus, trauma, regenerative anaemias and neoplasia other than MCT (Cayatte et al 1995). Peripheral mastocytosis was more probable and more striking in diseases other than MCT in 120 dogs studied (McManus 1999). Buffy coat smears are generally now not part of recommended staging for MCT.

FELINE MAST CELL TUMOURS

MCT in cats show a different distribution and biological behaviour than in the canine counterpart.

Cutaneous MCT

MCT is the second most common cutaneous tumour in the cat and accounts for 2–15% of all feline tumours (Buerger & Scott 1987, Molander-McCray et al 1998).

Two distinct forms have been recognized:

- more typical mastocytic MCT, histologically similar to canine MCT
- less common histiocytic MCT; morphologically the cells appear histiocytic.

Overall mean age is 8–9 years with no confirmed sex predilection. The histiocytic form is seen primarily in young cats (mean 2.4 years) while the mastocytic form has a mean age of 10 years. Breed predisposition is seen in Siamese cats (Macy & MacEwen 1989).

Mastocytic MCT

Mastocytic MCT can be either compact or diffuse on presentation.

- *Compact*: well-differentiated homogeneous population of mast cells with basophilic round nuclei, ample eosinophilic cytoplasm and distinct cell borders. Eosinophils are frequently present. They account for the majority of cases and are associated with more benign behaviour.
- *Diffuse*: anaplastic mast cells with larger nuclei (more than 50% of cell size), 2–3 mitosis/high-power field. The mast cell population seen is non-homogeneous, with marked variations in cell size; mononuclear and multinucleated giant cells and eosinophils are commonly seen. These MCT are behaviourally more malignant than the compact form.

Histological grade (used in dogs and highly predictive of outcome and behaviour) provided no prognostic information for cats in two series (Buerger & Scott 1987, Buss et al 1996).

Histiocytic MCT

These MCT are characterized by the presence of histiocytic-like cells with vague cytoplasmic granularity (comprising the majority of cells present), together with randomly scattered lymphoid aggregates and eosinophils. As mast cells comprise only 20% of cells present, the histiocytic form of MCT can be

misdiagnosed as granulomatous nodular panniculitis or deep dermatitis. Spontaneous regression can occur over a period of 4–24 months (Chastain et al 1988, Wilcock et al 1986).

Immunohistochemistry

All feline MCT are vimentin positive and the majority are positive for alpha-1 antitrypsin (Fondevila et al 1990). The majority of feline cutaneous MCT are behaviourally benign with the metastatic potential ranging from 0 to 22% (Buerger & Scott 1987, Carpenter et al 1987, Johnson et al 2002, Wilcock et al 1986). The majority of cases that do develop metastases or recurrence are the diffuse anaplastic MCT (Holzinger 1973).

Clinical signs

The most common clinical sign is the presence of a skin lump that can be:

- a solitary, raised, firm, well-circumscribed, alopecic nodule (Buerger & Scott 1987, Carpenter et al 1987, Miller et al 1991, Wilcock et al 1986), often white but can be pink and erythematous; in approximately 20% of cases there are multiple nodules and superficial ulceration is seen in approximately 25% of cases
- a flat, pruritic, plaque-like lesion, similar to eosinophilic plaques
- discrete subcutaneous nodules.

Distribution

Head and neck are the most common sites, then trunk and limbs (Buerger & Scott 1987, Carpenter et al 1987, Miller et al 1991). Often MCT of the head involve the pinnae near the ear base.

Intermittent pruritus and erythema are common, trauma can cause ulceration and Darier's sign has been reported (Macy 1986). Affected cats are usually otherwise healthy. Cutaneous MCT of spontaneously regressing histiocytic form are usually multiple, firm, alopecic, pink, not pruritic and sometimes ulcerated subcutaneous nodules (Chastain et al 1988, Miller et al 1991).

Diagnostic work-up

FNA is usually diagnostic for mastocytic MCT, but histiocytic MCT may require biopsy for confirmation.

Treatment and prognosis

Surgery is the treatment of choice for mastocytic cutaneous MCT. Most are behaviourally benign and wide surgical margins may not be as critical as in the dog. In general, where an adequate margin of excision has been obtained, and if the tumour is solitary, the prognosis is good.

In the authors' experience, incompletely resected MCT respond well to hypofractionated radiotherapy, although this is rarely required, it should be considered in cats where the location has made complete excision impossible, e.g. the head. Radiotherapy as sole treatment for a small number of cats with MCT on the head not amenable to surgery resulted in complete remission. As the tumour-free margin in cats is smaller than that required in dogs, and MCT are seen less frequently in cats, large numbers of patients treated with radiotherapy are not available for analysis. However, anecdotally, radiotherapy is an option for difficult surgical cases and consultation with a radiation oncologist is recommended in these instances.

Local recurrence rates of 0–24% have been reported with surgery alone (Buerger & Scott 1987, Buss et al 1996, Carpenter et al 1987, Johnson et al 2002, Wilcock et al 1986). Brachytherapy (Strontium-90) has been reported to be beneficial for cats with solitary cutaneous MCT (Turrel et al 2006).

For diffuse (anaplastic) mastocytic MCT a more aggressive approach, similar to canine MCT, may be prudent, as these have higher rates of recurrence and metastasis (Holzinger 1973). However, the efficacy of chemotherapy in feline MCT has not been established. A recent report (Rassnick et al 2008) showed a 50% response rate to CCNU (50–55 mg/m^2). Cases included both cutaneous and visceral disease.

For cats with multiple cutaneous mastocytic MCT the prognosis is guarded. These cats can become literally covered in cutaneous nodules. Personally, the author (SN) has found chemotherapy unrewarding, and in three cats treated with CCNU at 50 mg/m^2 there was little improvement. Rassnick et al (2008) also reported a poorer response in cats with multiple cutaneous MCT. Prednisolone as a palliative measure may be of some benefit.

In young cats with multiple histiocytic tumours, close monitoring is usually recommended as the majority spontaneously regress.

Visceral MCT

Visceral MCT as the primary site are more frequently seen in the cat than the dog, with up to 50% of MCT being of visceral origin in some series (Carpenter et al 1987, Neilson & Cole 1961).

A splenic form ('lymphoreticular MCT') represents the most common differential for splenic disease in cats. In one study, 15% of 455 spleens on post-mortem were positive for MCT (Spangler & Culbertson 1992). For cats with splenic MCT the mean age is 10 years, with no breed or sex predilection (Carpenter et al 1987).

MCT is the third most common primary intestinal tumour in cats, lymphoma the most common and adenocarcinoma the second most common. No breed or sex predilection has been recognized. This is generally seen in older cats with a mean age 13 years (Bortnowski & Rosenthal 1992).

The aetiology is unknown. There is no association with feline leukaemia virus (FeLV), feline immunodeficiency virus (FIV) or feline infectious peritonitis (FIP).

Clinical signs

These include anorexia, lethargy, vomiting, diarrhoea, weight loss and distended abdomen.

Physical examination

In many cases intestinal MCT are palpable as a discrete mass. Splenomegaly is the most common finding for patients with splenic MCT. Other findings are dependent on the presentation of the patient, e.g. pallor due to bleeding or anaphylactic shock, abdominal distension due to ascites, etc.

Multiple organ involvement and widespread metastasis are more common for visceral (intestinal and splenic) than for

cutaneous MCT. In one necropsy study of 30 cats with splenic MCT, metastasis to liver, visceral lymph nodes, bone marrow, lung and intestine was seen (Carpenter et al 1987). Peritoneal and pleural effusions containing eosinophils and mast cells occur in about 30% of cases (Carpenter et al 1987), bone marrow involvement in about 20% (Feinmehl et al 1992), and peripheral blood mastocytosis in about 40% of cats (Carpenter et al 1987).

Splenic MCT

Two forms are recognized (Hanson et al 2001, Sato & Solano 2004):

- diffuse infiltration resulting in splenomegaly
- nodular form, seen less frequently.

In one report, 18% of cats with cutaneous MCT went on to develop splenic disease (Carpenter et al 1987).

Diagnostic work-up

Abdominal ultrasound is the modality of choice to identify splenic MCT and facilitate staging (RLN and liver). An FNA of the spleen is indicated and the majority of MCT are identified in this manner. Other common differentials for splenomegaly include lymphoma, myeloproliferative disease, accessory spleen, haemangiosarcoma, hyperplastic nodules and splenitis. If peritoneal effusion is present, cytology is indicated and the fluid may contain large numbers of eosinophils or mast cells. Routine haematology and biochemistry are indicated, in addition to a coagulation profile. Up to 50% of cats with splenic MCT have a positive buffy coat and bone marrow (Carpenter et al 1987, Feinmehl et al 1992). Peripheral mastocytosis can be striking, with up to 32 000 cells/ l having been reported (Carpenter et al 1987). A bone marrow aspirate completes staging in these patients.

Treatment and prognosis

The treatment of choice for cats with splenic MCT is splenectomy. In cats with no involvement of the RLN or liver, or a malignant effusion, the prognosis is good, with survival times of greater than 1 year with no other treatment (MST 12–19 months) (Carpenter et al 1987, Feinmehl et al 1992, Guerre et al 1979). Interestingly, even patients with systemic mastocytosis can achieve these survival times (Liska et al 1979). Preoperative peripheral mastocytosis will often decline significantly with splenectomy, and rise again with disease progression. Frequent buffy coat smears are helpful to monitor for this progression.

The prognosis for patients with liver/lymph node involvement is poor. The efficacy of chemotherapy in these patients has not been established; cytotoxic drugs used have included prednisolone, vincristine, chlorambucil and cyclophosphamide. CCNU (50 mg/m^2) may be considered in patients with visceral metastases, although it has not been shown to be effective against cutaneous MCT.

Intestinal MCT

Feline intestinal MCT characteristically has an aggressive behaviour with widespread multiple organ involvement and a poor prognosis (Bortnowski & Rosenthal 1992, Carpenter et al 1987). The small intestine is the most common site (equally divided between duodenum, jejunum and ileum), with colonic involvement in less than 15% of cases. Intestinal lesions can be solitary or multiple, and there may be an accompanying peritoneal effusion containing many mast cells. Unlike the splenic form, intestinal MCT is not commonly associated with peripheral mastocytosis, but eosinophilia has been reported (Bortnowksi & Rosenthal 1992). Metastasis commonly occurs to mesenteric lymph nodes, liver, spleen, lung and bone marrow.

Clinical signs

Clinical signs can be similar to those seen in patients with splenic tumours, e.g. anaemia, anorexia, vomiting, diarrhoea, weight loss, abdominal distension, peritoneal and pleural effusions. PNS due to degranulation of MCT, often episodic in nature, can be seen and includes hypotensive shock, uncontrollable bleeding, gastrointestinal ulceration and respiratory distress.

Diagnostic work-up

Abdominal ultrasound is the diagnostic tool of choice to delineate an intestinal mass and stage for regional or distant metastases. In many cases FNA of an intestinal mass can be diagnostic. Additional tests are the same as for splenic MCT.

Treatment and prognosis

The treatment of choice for intestinal MCT is surgical excision with wide margins, including 5–10 cm normal bowel on either side of the lesion. Biopsies should be taken of liver and lymph nodes at surgery for staging purposes. Despite treatment, most cats with intestinal MCT die or are euthanized soon after diagnosis. The median survival time is 2 months.

Chemotherapy has not been shown to increase survival times in these patients; prednisolone can be used as palliative therapy. Occasional cases of solitary intestinal MCT without metastasis that have good survival times after surgical excision have been reported.

Other presentations of feline MCT

A cranial mediastinal form of MCT in cats has also been described.

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Sarcomas of the skin and subcutaneous tissues

Soft tissue or spindle cell sarcomas (STS)

In this section a general discussion of the STS family follows. The section is divided into canine and feline sarcomas to facilitate emphasizing some of the differences encountered in the two species, but the overall characteristics of STS will be described under canine sarcomas.

CANINE SARCOMAS

Introduction

The name 'sarcoma' is derived from the Greek word *sarkoma*, meaning 'fleshy growth', and virtually all members of the 'family' are derived embryologically from mesoderm. It is the primitive mesoderm that gives rise to the connective tissues of the body and STS include those tumours that arise from extraskeletal connective tissue whose function it is to connect, support and surround other discrete anatomical structures. Tumours of the Schwann cells are also included in this group, even though they arise from the neural tube of the primitive ectoderm.

STS are characterized by the possession of a pseudocapsule that is composed of compressed tumour cells providing no 'capsular' barrier to the local spread of tumour cells. Morphologically they are distinct, but because their biological behaviour is similar, the fine distinctions between these tumours are often no longer reported and they are described as STS without reference to the cell of origin. Tumours considered STS are listed in Table 20.1; other sarcomas that are found within the skin and subcutaneous tissues, including haemangiosarcomas (HSA) and histiocytic sarcomas (HS), are not considered as STS because of their more aggressive biological behaviour and are discussed separately. STS as a family typically have a low–moderate metastatic potential and predominantly spread haematogenously.

Incidence and risk factors

STS are relatively common tumours with a generally unknown aetiology. Sarcomas may develop in association with radiation, trauma, foreign bodies, orthopaedic implants, *Spirocerca lupi* infestation, and in cats with feline sarcoma virus, vaccines/other subcutaneous injections, and trauma (e.g. intraocular sarcoma) (MacEwen et al 2001). STS accounts for approximately 15% of all canine tumours (compared to 0.7% in humans) and are more common in medium to large breed dogs, of middle to older age (10 years). However, any age or breed of dog or cat can be affected. There is no sex predilection.

Clinical signs

STS will often appear as a single, soft to firm, rounded, non-painful, fixed or mobile subcutaneous mass in any site, including head and neck, but most often over the trunk or extremities. The distribution of STS has been reported as 40% trunk, 25% proximal to the knee, 12% proximal to the elbow, 7% distal to the elbow and 9% distal to the knee. STS demonstrate a variable growth rate, although most are commonly slow growing, with symptoms related to the location of the mass and the degree of invasion.

Diagnostic work-up

Initially, the clinician should perform a complete physical examination of the patient. The mass should be palpated to give an idea of site, size and fixation to underlying or adjacent structures. The regional lymph nodes (RLN) are also palpated for enlargement and fixation to underlying tissues (remember most STS will not metastasize via regional lymph nodes).

Fine needle aspirate (FNA) cytology of the mass should be performed. This is primarily to exclude other differential diagnoses such as mast cell tumour, infection, inflammation, lipoma, etc. In general, STS do not exfoliate well on FNA, and it is the more aggressive tumours that are likely to be positive for neoplastic cells on cytology. Often it is the absence of cells obtained from an aspirate that increases the suspicion of an STS and should then prompt a biopsy (see Chapter 5). In one study of 40 dogs with STS, FNA cytology obtained an incorrect diagnosis in 15%, a further 23% were non-diagnostic and only 62% were correctly diagnosed (Baker-Gabb et al 2003).

A definitive preoperative diagnosis and histopathological grade are obtained from tissue biopsy (punch, needle core, incisional). Tumour grade is important for predicting prognosis and for treatment planning. The biopsy tract should be positioned so that it is excised at curative-intent surgery, or included in the radiation field (without increasing the size of the radiation field). Excisional biopsies/marginal resections are not recommended. Subsequently, more aggressive surgery is required to achieve complete histological margins, with greater morbidity and expense than if incisional (wedge or core) biopsies were originally performed.

The survival time in dogs with STS is also shortened with multiple attempts at resection (Posterino et al 1988). The chance of a surgical cure is greatest with the first surgery (Banks et al 2003, 2004, Graves et al 1988, Kuntz et al 1997, Liptak

Table 20.1 Tumours considered members of the STS Family

Tissue of origin	Malignancy	Metastatic potential
Fibrous	Fibrosarcoma	+/++
Adipose	Liposarcoma	+/++
Schwann cell	Schwannoma/nerve sheath tumour	+/++
Pericyte	Haemangiopericytoma	+
Fibrous + giant cells	Malignant fibrous histiocytoma (does not stain positive for histiocytic markers)	+/++
Skeletal muscle	Rhabdomyosarcoma	++
Lymphatics	Lymphangiosarcoma	++
Smooth muscle	Leiomyosarcomas	+/++
Synovium	Synovial cell sarcoma	+/+++
Unknown	Anaplastic (poorly differentiated)	+++

+ low metastatic potential; ++ moderate metastatic potential; +++ high metastatic potential.

Table 20.2 Grading of STS

Grade	Degree of differentiation	Mitotic index*	Necrosis
Low (1)	Normal appearance	<10	None
Intermediate (2)	Histologically identifiable	10–19	<50%
High (3)	Undifferentiated	>19	>50%

Reproduced with permission from Kuntz et al (1997).
*Mitotic index: number of mitotic figures/10 high-powered fields (40×)

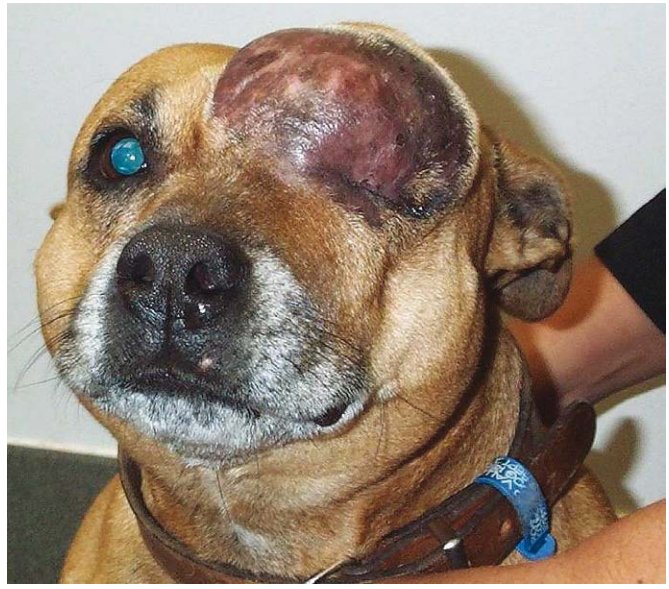

Figure 20.1 Large soft tissue sarcoma on the head of a Staffordshire Bull Terrier. (Courtesy R Straw.)

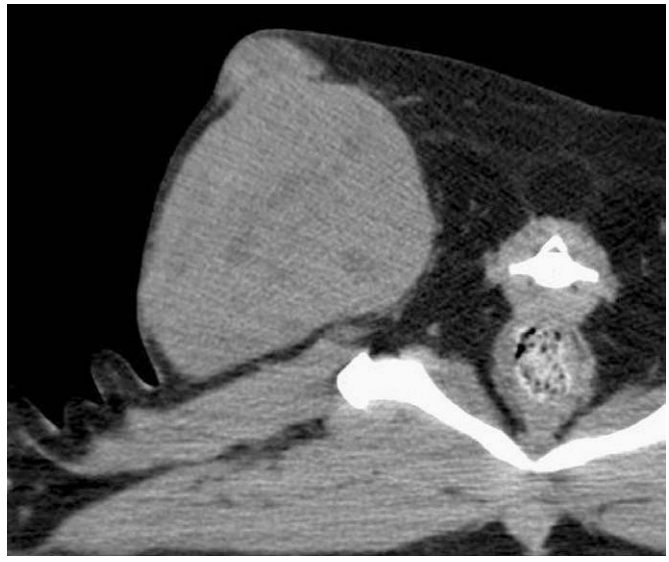

Figure 20.2 CT scan of large soft tissue sarcoma close to the tail base.

et al 2007, MacEwen et al 2001, Posterino et al 1988). As there is also a tendency for selection of more malignant cell populations with repeat surgeries, low-grade tumours can, with time, become more malignant and likely to metastasize.

The metastatic potential is reflected in the grade of STS; less than 10% grade I, 20% grade II and 50% grade III undergo metastasis (Kuntz et al 1997). High-grade (III) tumours are characterized by a higher mitotic rate, greater percentage necrosis and increased metastasis (Bostock & Dye 1980, Graves et al 1988, Kuntz et al 1997). Locally, these tumours tend to grow more rapidly, be more invasive and show higher rates of local recurrence (Bostock & Dye 1980, Graves et al 1988, Kuntz et al 1997) (see Table 20.2 for the staging system commonly used for canine STS). It should be noted that the significant improvement in the management of primary STS has resulted in a greater proportion of patients living many years after surgery, with the consequence that late metastases are seen.

Routine haematology, biochemistry and urinalysis are usually normal for dogs with STS that adhere to the traditional classification.

The most important tool for staging of metastatic disease is either thoracic radiographs or thoracic CT. Palpable RLN metastasis occurred in 0% in two studies (Banks et al 2003, 2004), and in 6% in another study (Kuntz et al 1997); however, FNA or biopsy of RLN should be performed in dogs with clinically abnormal lymph nodes (Liptak et al 2007).

Abdominal ultrasonography or other advanced imaging may also be employed to assist in further staging in selected cases. The surgeon and/or radiation oncologist may also benefit from further imaging of the local tumour. Routine radiography, ultrasonography, CT, MRI, nuclear scintigraphy or angiography may be useful for planning either the surgical approach or radiation therapy, especially for large fixed STS or STS in close proximity to vital structures (**Figure 20.1**). CT three-dimensional (3-D) images are especially useful for surgical planning, particularly if an aggressive resection with curative intent is planned (**Figure 20.2**).

Treatment

After staging is complete, treatment options are considered. This is because the presence of metastatic disease changes the goal of treatment to palliation rather than potential cure. In the absence of metastatic disease, the treatment of choice is surgical excision of the tumour with wide margins and one fascial plane deep. The most important surgical consideration is not to be misled by the pseudocapsule into shelling these tumours out. These peripheral cells can be more aggressive and may be responsible for the extensive invasion into adjacent normal tissues characteristic of STS. If these potentially more aggressive peripheral or deeply invasive cells are left behind, tumour regrowth is expected. Incomplete resection of canine STS has been reported to result in a probability of local recurrence of 60% within the first 12 months (Bostock & Dye 1980). In another study, 28% of dogs with incomplete STS resection had local recurrence, and were over 10 times more likely to have local recurrence than dogs with complete excision (Kuntz et al 1997).

Surgical resection with wide margins

It is generally well accepted that surgical resection with wide margins provides the best chance for long-term control, survival and cure for patients with STS. 'Wide margins' refers to the minimum recommended surgical margins, i.e. 3 cm of grossly normal tissue lateral to the tumour and at least one fascial layer deep to the tumour (Baker-Gabb et al 2003, Banks et al 2003, 2004, Dernell et al 1998, Kuntz et al 1997, Posterino et al 1988). Surgical resection with wide, histologically complete, quantitatively evaluated surgical margins resulted in 90–100% local disease control rate, and a 90–93% 1-year disease-free survival in two studies (Evans 1987, McChesney et al 1989).

Another study reported that canine STS removed with attempted wide margins, regardless of completeness of excision, had an 85% rate of local tumour control with a median time to recurrence of 368 days (Kuntz et al 1997). In a third study, 79% of canine STS resected with wide, complete, histological margins were controlled for 2 years (Posterino et al 1988). In 56 dogs with liposarcomas, surgical dose was the only factor significantly associated with survival time (Baez et al 2004). Resection of liposarcomas with wide margins achieved a median survival time (MST) of 1188 days, compared to 649 days for marginal excision and 183 days for incisional biopsy.

As a chance for cure rests with an adequate surgical dose, referral to a specialist facility should be considered for difficult cases, especially where advanced imaging facilities are required. Achieving wide clean margins can be a surgical challenge, but as it affords the best prognosis, it is a worthy undertaking. As mentioned above, associated biopsy tracts and any areas of fixation (e.g. bone, fascia) should be removed en bloc with the tumour (**Figure 20.3**).

Surgeons should familiarize themselves with cutaneous reconstructive techniques. Local pedicle flaps (e.g. advancement, rotation, transposition) and axial pattern flaps of the head and neck (caudal auricular, omocervical, thoracodorsal) may assist in closing large skin deficits of the head and neck. Detailed, valuable descriptions of skin flaps are found in Pavletic's *Atlas of Small Animal Reconstructive Surgery* (1999).

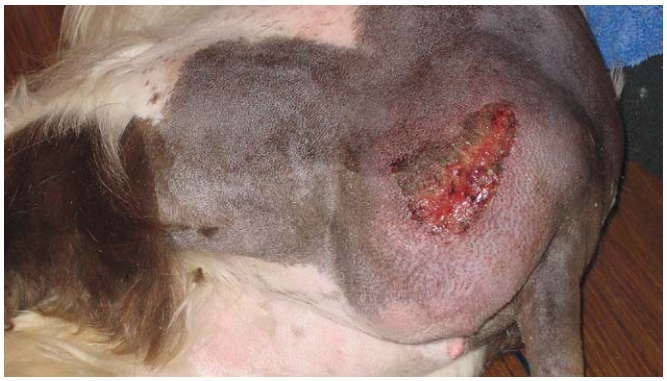

Figure 20.3 Biopsy of large soft tissue sarcoma.

It should also be remembered that for STS of the distal extremities amputation is an option for achieving wide surgical margins. In most situations client preference is to save the limb if possible, but for large tumours, those that are circumferential, where radiotherapy may not be accessible, or where financial considerations impact on future treatment, amputation is a very cost effective and acceptable procedure. It should also be considered in patients that have failed cytoreductive surgery and/or radiotherapy.

Marginal resection and adjuvant radiation therapy

If the tumour cannot be excised with wide margins, marginal resection followed by adjuvant radiotherapy is recommended to increase disease-free interval and survival time. Generally, the use of radiation is restricted to the extremities and head and neck where the achievement of surgical margins is more complicated and recurrence more difficult to manage. Local control is better with higher cumulative doses, but the optimal treatment protocol has not yet been determined (Forrest et al 2000, McKnight et al 2000).

Marginal resection followed by fine fractionated megavoltage radiotherapy has been reported in two studies to result in a 16% local recurrence rate with a median time to recurrence of 700 days to more than 798 days (Forrest et al 2000, McKnight et al 2000). Radiotherapy can be utilized prior to surgery in an attempt to decrease tumour volume to allow a wide surgical excision. The use of radiotherapy should ideally involve a team approach with the surgeon and the radiotherapist from the outset, rather than employing radiotherapy as a rescue procedure. Consideration must be given to potential complications of radiation to the structures of the head and neck (e.g. eyes, spinal cord, brain), which may lead to oronasal fistula, bone necrosis, etc. (Chapter 7).

Radiation therapy alone

Radiotherapy alone is generally considered palliative. It may achieve local control in 48–67% of tumours in the first 12 months, with higher cumulative radiation doses resulting in better control rates. However, this rate of local STS control is reduced to 20–33% at 2 years (McChesney et al 1989).

Chemotherapy

Situations in which chemotherapy should be considered include metastatic disease and dogs with high-grade STS (MacEwen et al 2001). However, the efficacy of chemotherapy in the management of sarcomas of the head and neck is not supported by data from previous trials. One report in the literature did not show an increase in survival time (Selting et al 2000) and most showed partial responses of a short duration (Henry et al 1999, Ogilvie et al 1989, 1991, Rassnick et al 2000).

Metastatic disease

The presence of metastatic disease changes treatment goals considerably. Management should be with intent to palliate rather than to cure. Therefore aggressive surgery and/or radiation therapy is generally not warranted. The role of pulmonary metastectomy for STS is unknown.

Prognostic factors for local tumour recurrence

Prognostic factors for local tumour recurrence include tumour location, size, completeness of excision and grade. STS in superficial sites or the extremities have a better prognosis than those which are deep, truncal, invasive or close to the spinal cord. In these situations, there is a diminished ability to achieve complete surgical resection.

Incomplete resection is over 10 times more likely to result in local disease recurrence (Kuntz et al 1997). Thickness of deep margin and tumour grade (low and intermediate more favourable) are prognostic factors for local recurrence (Banks et al 2003, 2004, Bostock & Dye 1980, Kuntz et al 1997, Posterino et al 1988). Tumours that are freely movable may have a more favourable prognosis than those fixed to underlying tissues (Banks et al 2004). Increased intratumoral microvessel density (IMD), a measure of tumour angiogenesis, is associated with higher histological grade, necrosis scores and mitotic scores for canine STS (Luong et al 2006).

Prognostic factors for survival

Uncontrolled local disease is most often the cause of tumour-related death from STS. Mitotic rate and percentage tumour necrosis were the variables significantly associated with survival time on multivariate analysis in one article (Kuntz et al 1997). Mitotic rate (among other factors) was a significant prognostic factor for survival (univariate analysis) in another article. However, the only significant prognostic factor for survival on multivariate analysis was an increased argyrophilic nucleolar organizing regions (AgNOR) score, an indicator of nuclear activity and cellular proliferation (Ettinger et al 2006).

Other prognostic factors for overall survival include tumour size, completeness of excision, degree of differentiation, histological grade and local tumour control (Kuntz et al 1997). Increased IMD was not prognostic for survival (Luong et al 2006). Dogs with non-oral STS treated with wide surgical resection had an MST of 1416 days. Similar dogs treated with marginal surgical resection combined with adjuvant megavoltage radiation showed a 2270-day MST (Forrest et al 2000, Kuntz et al 1997).

Sarcomas that are typically members of the STS family but with distinguishing features

Myxosarcomas

These rare STS deserve a special mention. What distinguishes these tumours from other members of the STS family is the production of large amounts of mucinous material. This means that on examination they may appear fluid, almost cyst-like, and an FNA can be very misleading, yielding mucinous fluid that can be interpreted as a cyst. Biologically, they behave as any 'classical' STS, i.e. that is locally invasive, but with a low–moderate metastatic rate. Locally, however, they can be extremely challenging because the mucinous secretion makes it extremely difficult for the surgeon to determine tumour boundaries. Incomplete resection of a myxosarcoma should be treated as for any other STS with adjuvant radiation.

Lymphangiosarcomas

Again, these are rare tumours that warrant special mention. As with myxosarcomas, diagnosis may be difficult in the initial phases as the patient may present with diffuse swelling or 'weeping' skin. Lymphoedema is characteristic of these tumours and surgical control can be frustrating because of the diffuse nature of the tumour itself as the lymphoedema spreads. They are seen typically on the distal extremities and in cats aggressive lymphangiosarcomas have been seen on the ventral abdomen. Advanced imaging (MRI/contrast-enhanced CT) may be beneficial in delineating the extent of the tumours, but prognosis is dependent on adequate excision or combination treatment with radiation.

Other sarcomas

Haemangiosarcomas (HSA)

HSA of the skin and subcutaneous tissue also deserve a special mention. Small primary cutaneous tumours may be either primaries or secondaries, so a full diagnostic evaluation is indicated. Cutaneous metastases from visceral HSA carry a poor prognosis. Small primary cutaneous HSA that can be completely excised with margins have a good to fair prognosis as the metastatic rate is low. Large, deeply infiltrated HSA are aggressive and should be managed like STS with excision with wide margins, and if margins are not achieved, adjuvant radiotherapy. The risk of developing distant metastases is high so staging prior to surgery is indicated. These tumours are usually primaries and the major metastatic site is the lung. In these patients the authors recommend adjuvant chemotherapy (doxorubicin).

Multiple cutaneous HSA is a further manifestation that is rarely encountered but can be frustrating to deal with. Typically, these tumours are small and initially surgical excision is the treatment of choice; however, this may become impossible due to the large numbers of tumours that may develop. Doxorubicin may be beneficial; however, reports on this are lacking. Intralesional interferon alpha (IFN-α) is effective in human paediatric patients with large inoperable haemangiomas and may have application for veterinary patients.

Sarcomas affecting the joint

Synovial cell sarcomas

Synovial cell sarcomas are malignant tumours that arise from the mesenchymal cells within the tenosynovial tissues of joints, bursas and tendon sheaths. The most commonly affected joint is the stifle, followed by elbow, shoulder, carpal, tarsal and hip joints. The mean age at presentation is 6–8 years, with Flat-coat Retrievers (FCR) and males over-represented. Previous reports have shown that up to a third of dogs have metastasis to regional lymph nodes and lungs at the time of diagnosis, and ultimately up to 50% of dogs will develop metastasis.

Previously, synovial cell sarcoma was the most commonly diagnosed neoplasm of the joint, but other sarcomas, particularly histiocytic sarcomas, are now more prevalent. In many cases immunohistochemistry is required to distinguish these tumours. Knowing the predisposition of FCR to develop sarcomas, particularly HS, the above over-representation of this breed for developing synovial cell sarcomas may require modification in the light of current knowledge of Histiocytic Sarcomas (HS) (see below).

Clinical signs and diagnostic work-up

Typical presentation is lameness. Physical examination of the affected joint will elicit pain and effusion. Palpation of regional lymph nodes is required and an FNA if enlarged.

Radiographs of the joint will often show soft tissue opacity adjacent to the joint; mineralization is rare. Bone involvement may be seen in some cases that can be either punctate lysis of bone due to invasion by tumour cells or smooth due to pressure necrosis from tumour. Thoracic radiographs or CT are required to check for thoracic metastasis.

Definitive diagnosis requires biopsy, as synovial cell fluid is rarely diagnostic and usually is consistent with low-grade chronic inflammation. Techniques for obtaining a biopsy include open wedge or Jamshidi needle.

Histologically, synovial cell sarcomas have two distinct populations of cells, epithelioid and spindle. However, in many cases, this morphological distinction is not sufficient to differentiate synovial cell from other sarcomas. Immunohistochemistry is recommended, with synovial cell sarcomas staining positive with cytokeratin antibody AE1/AE3, HS with CD18 antibody and malignant fibrous histiocytomas with smooth muscle actin antibody.

Treatment

The treatment of choice for sarcomas of the joint is high amputation of the affected limb. The role of radiation is unknown, but may be conceived as palliative treatment for patients in pain in which amputation is not an option, either because of other orthopaedic problems or client preference.

The role of chemotherapy is also unknown, but in humans chemotherapy does not improve overall survival times. Should chemotherapy be considered in a veterinary patient the drug of choice is doxorubicin. The patients most likely to receive benefit from chemotherapy would be those with high-grade tumours.

Prognosis

Prognostic factors include:

- clinical stage
- histological grade
- treatment.

Clinical stage

- T1: well defined with no invasion into local structures
- T2: involving soft tissues
- T3: invading bone and joint.

Local disease, irrespective of stage, has not been shown to be prognostic; however, metastatic disease (either regional or distant) warrants a poor prognosis with an MST less than 6 months.

Histological grade

Grade is prognostic with MST of greater than 48 months for grade I tumours, 36 months for grade II tumours and 7 months for grade III tumours (Vail et al 1994).

Treatment

Aggressive surgery is indicated, as local tumour control is poor with conservative approaches. No treatment results in survival times of 93 days, 455 days with conservative treatment and 840 days with amputation (Fox et al 2002). The possibility of combining cytoreductive surgery and radiotherapy has not been evaluated.

Other sarcomas that affect the joint include HS (see below), malignant fibrous histiocytoma, synovial myxosarcoma, osteosarcoma, fibrosarcoma, haemangiosarcoma, liposarcoma and undifferentiated sarcomas.

Histiocytic sarcoma (HS)

HS deserve a special mention and because of the various presentations of histiocytic disease seen in the dog, including HS, these tumours will be encountered in other chapters. The histiocytic diseases are both extremely interesting and for many veterinary surgeons an extremely confusing set of disease syndromes that range from the benign cutaneous histiocytoma to the extremely aggressive disseminated HS. A major problem to understanding these complex disease syndromes is that our knowledge of their importance in veterinary oncology has only been appreciated relatively recently, primarily due to the emergence of immunophenotyping to characterize tumours that might previously have been misdiagnosed based on haematoxylin and eosin (H&E) staining of biopsy material. The reader is advised to be careful in evaluating the old literature as this is a fast-moving area and our appreciation of histiocytic disease is constantly changing. The reader is referred to Moore & Affolter (2005). For more information on HS and to the appropriate chapters in this text.

Origin of histiocytic cells

Histiocytes differentiate from CD34+ precursors into macrophages and dendritic cells (DC), e.g. Langerhans cells. Dendritic cells are antigen-presenting cells with a wide distribution through epithelial sites (cutaneous and mucosal) and these cells constantly migrate through the paracortical areas of lymph nodes.

The recognition of histiocytic disorders in the dog has increased considerably over the past few years and what was

once thought to primarily affect Bernese Mountain Dogs (BMD) is now recognized in a number of breeds and with prognosis dependent upon the clinical presentation.

Currently, four histiocytic diseases are recognized in the dog:

- canine cutaneous histiocytoma complex (see Chapter 18)
- canine reactive histiocytosis (see Chapter 18)
- histiocytic sarcoma (HS)
- malignant histiocytosis (MH) now known as disseminated HS (see Chapter 23).

HS is seen in a number of breeds including BMD, FCR, Rottweilers, Golden Retrievers and others. HS of the spleen may be seen as an isolated lesion, multiple lesions within the spleen, or as disseminated disease involving multiple organs (see Chapter 23).

Histiocytic neoplasia that originates at a single site is known as HS. This is commonly found on the extremities or associated with joints, and should be treated early with surgical excision or amputation of the affected leg (**Figure 20.4**). Disseminated HS occurs when the tumour has spread beyond the regional lymph node and is more likely to occur when HS arises internally, e.g. spleen or lung. This was previously known as MH.

Primary HS can occur in a number of organs in addition to the skin, subcutis and periarticular tissues, including spleen, lymph node, lung and bone marrow. Secondary sites include liver and lung (with splenic primary) and hilar lymph node (with lung primary). The central nervous system (CNS) can be involved as either a primary or a secondary site.

Clinical signs and diagnostic work-up

Clinical signs depend on location and stage of disease; for internal HS the reader is directed to the relevant chapters.

For patients with periarticular HS the initial presenting sign is usually lameness and the diagnostic evaluation is similar to patients with synovial cell sarcomas (see above). However, with HS, in addition to evaluation of regional lymph nodes and thorax, an abdominal ultrasound/contrast-enhanced CT is advised to rule out disseminated HS. Regenerative and non-regenerative anaemias may be seen in patients with disseminated HS.

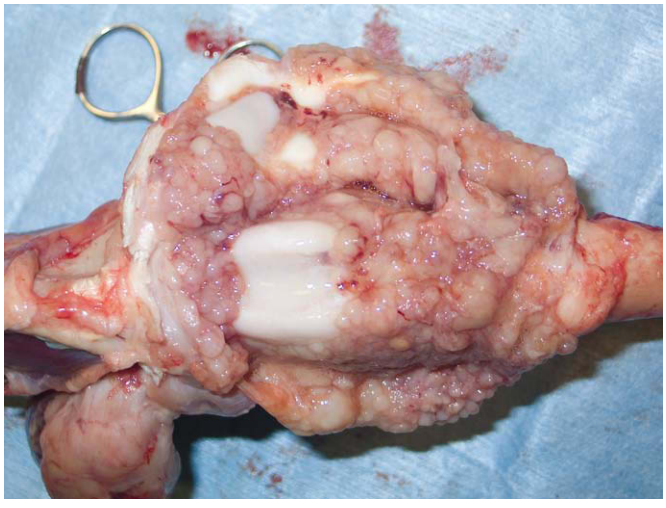

Figure 20.4 Histiocytic sarcoma affecting the stifle of a large breed dog.

Localized HS affecting the skin and subcutis appears as a solitary cutaneous to subcutaneous lump that is non-painful and may be growing rapidly. FNA shows a population of round cells, and biopsy is required for diagnosis. In many instances immunohistochemistry is required for identification of histiocytic tumours from cutaneous lymphomas.

Treatment

The treatment of choice for HS in the absence of metastatic disease is surgical excision with margins. For HS affecting the periarticular tissue this means amputation of the limb; for cutaneous HS surgical excision with margins is recommended. If surgical margins are not achieved, then adjuvant radiotherapy is required.

Because of the possibility of metastatic disease in these patients, the authors advise a short course of adjuvant chemotherapy for patients with large invasive tumours, i.e. those involving the periarticular tissues or those requiring radiotherapy in addition to surgery. The chemotherapeutic drug of choice is CCNU, with a reported response rate of 46% (Skorupski et al 2007). The chemotherapeutic regimen recommended by the authors is three cycles of CCNU (60–70 mg/m^2) at intervals of 3 weeks and monitoring at 3-monthly intervals on completion of chemotherapy. For other patients with isolated HS that is adequately surgically excised chemotherapy is not given routinely but close monitoring for new lesions, local recurrence or metastasis is recommended.

For patients that present with significant metastatic disease the prognosis is poor, although CCNU may be of some benefit in these patients. For those with a solitary lymph node or pulmonary metastases, good responses with CCNU have been achieved (personal experience). For those breeds with a known predisposition to develop aggressive histiocytic disease (FCR and BMD) the authors always recommend CCNU chemotherapy.

FELINE SARCOMAS

Dog and cat STS behave similarly, with the exception of feline vaccine-associated sarcoma (VAS), feline intraocular sarcoma, and feline virally induced multicentric fibrosarcoma. Spontaneous STS are much less common in the cat compared to the dog, as are other sarcomas that involve the skin and subcutaneous tissues.

Feline intraocular sarcoma

This will be discussed in Chapter 25.

Feline virally induced fibrosarcoma complex

Feline virally induced multicentric fibrosarcoma is seen in young feline leukaemia virus (FeLV) positive cats. These cats present with tumours, often ulcerated, in multiple locations that grow extremely rapidly (doubling time 12–72 hours) and causing debilitation. Only 2% of cat fibrosarcomas are virally induced. The feline sarcoma virus is a hybrid of FeLV DNA provirus with cat proto-oncogenes.

Prognosis is poor, and cats die quickly due to progressive disease. Metastasis occurs in 30% of cases. Chemotherapy, surgery and radiation have been tried, but none has shown a significant survival benefit to the patient because of rapid progression and tumour recurrence.

Feline vaccine-associated sarcoma (VAS) also known as feline injection-site sarcoma (ISS)

Aetiology

These are thought to arise as a consequence of an excessive inflammatory response to a subcutaneous injection resulting in uncontrolled fibroblast growth and eventual tumour formation (Richards et al 2005), which can occur from 4 weeks to 10 years after vaccination (Burton & Mason 1997). Similarities exist between the transition from inflammation to neoplasia seen in feline intraocular sarcomas and VAS (Esplin et al 1993, Evans 1987, Hendrick & Brooks 1994).

This over-reactive inflammatory response to either injection or local trauma is likely to have a genetic basis, as some cats have a genetic predisposition to the development of VAS (Banerji et al 2007). Although originally described as associated with vaccination, it is now known that any source of chronic inflammation appears to be capable of predisposing some cats to tumour development and it has been suggested that these tumours may be more appropriately classified as 'injection site sarcomas' (Kass et al 2003).

Overexpression of the tumour suppressor gene *p53* has been reported in a number of studies (Hershey et al 2005, Nambiar et al 2001), in addition to the presence of epidermal growth factor/receptor and platelet-derived growth factor/receptor on tumour cells from injection sarcomas but not found on patients with non-injection sarcomas. Simultaneous injections at the same site increase the likelihood of tumour formation (Macy & Hendrick 1996). The development of VAS had been linked primarily with the adjuvanted vaccines because of their association with the most intense inflammatory response (McEntee & Page 2001). Genetic alterations found in some cats with VAS also have a negative influence on prognosis (Banerji & Kanjilal 2006).

Vaccination recommendations

In the USA the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) was formed a number of years ago to investigate the aetiology of VAS and provide recommendations for the prevention and treatment of these tumours. VAFSTF recommends that no vaccine is given in the interscapular area and this is a recommendation that, if followed in other countries, would improve our ability to handle these tumours significantly:

- rabies vaccines are given in the distal right hind leg
- FeLV vaccines are given in the distal left hind leg
- all other vaccines are given on the right shoulder.

This is to allow earlier detection of a lump, and amputation of a limb, rather than extensive surgeries to the neck, head, chest and body wall for radical VAS resection. VAS is then more amenable to surgical resection with wide margins, subsequently reducing morbidity and the need for repeated surgeries or adjuvant radiation.

Cats identified as having a greater risk of developing VAS due to *p53* gene mutations may potentially be better managed or avoid the development of VAS by modification of the administration (e.g. locations, types, volumes, frequencies) of subcutaneous injections or implants. The recent development of multicomponent non-adjuvanted vaccines may, by reducing inflammation associated with routine vaccination, lead to the development of fewer cases of VAS (Day et al 2007).

Other practical considerations are to determine the frequency with which vaccination is required and where possible, based on the license of the vaccine, legal and life style issues, move away from annual boosters to revaccination intervals of up to 3 years.

Behaviour

VAS are exceptionally locally invasive and even radical resection may not result in permanent control of local tumour, although the disease-free interval can be prolonged. The metastatic potential of VAS is greater than that seen with non-injection sarcomas, with a reported metastatic rate of up to 25% (median time to metastasis is 265 days) (Romanelli et al 2008), although most patients tend to die of uncontrolled local disease (usually euthanized due to local tumour growth and associated poor quality of life). As with most sarcomas, better control of local disease may result in more patients being recognized with metastasis.

The histological appearance parallels clinical behaviour, as only 6% are low grade and up to 60% high grade (Kuntz, unpublished data). Fibrosarcomas, rhabdomyosarcomas, malignant fibrous histiocytomas, undifferentiated sarcomas, extraskeletal osteosarcomas or chondrosarcomas may all develop as a result of previous vaccination (Cohen et al 2001, Heldman et al 2000, Hendrick & Brooks 1994).

Diagnostic work-up

VAS shows no age or breed predisposition and can occur at any age. The number of injections over time is not known to influence the development of these tumours as cats may develop a VAS after a single injection.

Any swelling/lump in an area of previous injection should warrant concern about the probability of a sarcoma. These tumours are typically firm, non-painful and may or may not appear movable; often they are fast growing (**Figure 20.5**). An FNA of the lump can assist in diagnosis (and help to rule out

Figure 20.5 Large interscapular sarcoma on a cat.

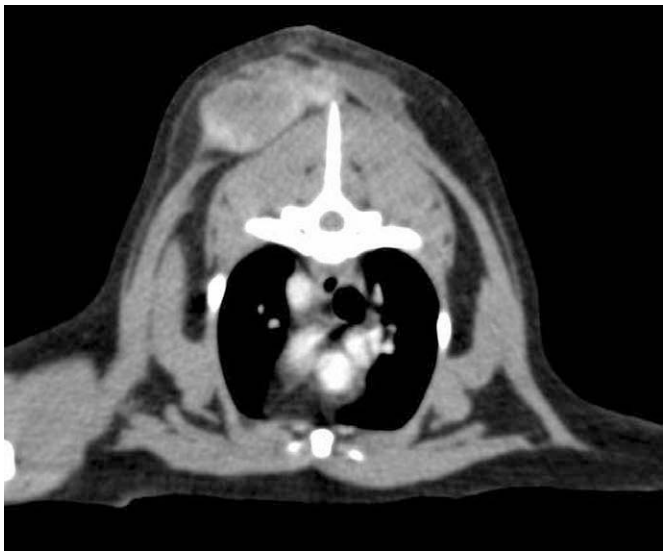

Figure 20.6 Contrast-enhanced CT scan of an interscapular vaccine-associated sarcoma.

other causes of a subcutaneous lump), but it is important to remember that mesenchymal cells do not exfoliate well so a negative aspirate does not mean that it is not a sarcoma. In such instances an incisional biopsy may be indicated. The guidelines for incisional biopsies are outlined in Chapter 5, because it is essential not to compromise the definitive surgery with the position of the biopsy tract.

For any patient with a suspected VAS a routine database should be established. Thoracic radiographs/CT are indicated to rule out metastatic spread. Plain radiographs of the primary may be unrewarding as to the extent of the tumour, particularly in the interscapular region, and advanced imaging (CT/MRI) is advised to allow for presurgical planning (**Figure 20.6**).

Treatment

The treatment of choice is surgical excision with wide margins. The VAFSTF recommends masses at vaccination sites should undergo definitive treatment if they are:

- more than 2 cm in diameter, *or*
- increasing in size more than 4 weeks after vaccination, *or*
- still present ≥3 months after vaccination.

As we know, smaller disease has a more favourable prognosis for the simple reason that surgery has a greater chance of achieving good surgical margins and with less morbidity for the patient. Once the clinician has a presumptive diagnosis of VAS, expedient referral to a specialist surgeon should be recommended (time is of the essence with VAS as they grow so rapidly). It is the authors' recommendation, based on long experience, that an experienced oncological surgeon should perform the first attempt at any surgical resection of a VAS! The general practitioner should avoid performing either an excisional biopsy or an incomplete resection on a suspected VAS, because the chances of attaining prolonged survival with radical surgery will then be greatly reduced.

The volume of VAS measured using contrast-enhanced CT is approximately double the volume palpated clinically (McEntee & Page 2001). In other words, these tumours are much larger than they appear, and are very difficult to remove with clean margins, although this is considered possible. Contrast-enhanced 3-D imaging can be used to assess the feasibility of a wide surgical resection. Planned marginal excision and radiation should also be preceded by contrast-enhanced CT or MRI to minimize the chance of tumour miss within the radiation field. Also, if adjuvant radiation is planned, a marginal resection should be performed at the referral centre where the radiation will be delivered, so that the radiation oncologist can accurately plan treatment.

Tumours removed from the interscapular area deserve specific mention when considering marginal resection and radiation. Treatment planning in this area is complex, as underlying structures such as lung (very radiation sensitive) and spinal cord will be incorporated into the treatment plan and present the radiation oncologist with a number of considerations not found when irradiating sarcomas on the extremities. Radiation in this region is primarily reserved for preoperative shrinkage of large tumours or small fields where a very specific margin has been identified, or as palliative therapy for inoperable tumours. Electrons may be beneficial for residual disease, but megavoltage radiotherapy for microscopic VAS is potentially high risk and should not be considered a routine option. Again, this problem could easily be avoided by changing the practice of vaccinating in the interscapular area.

What do we mean by radical surgical resection and how are VAS different in this respect from other STS?

Typically for STS the margins required are 2–3 cm laterally and one fascial plane deep. Common sense should tell us that the larger the tumour and the higher the grade, the bigger the margin required, so when it comes to looking at the surgical margins required for VAS there have been a number of studies to evaluate just how 'big' is big.

'Wide' margins

The initial recommendation of VAFSTF for wide surgical margins was 2 cm margins and one fascial plane deep. This is now thought to be inadequate because, with these margins, only 50% of patients were considered to have a clean resection (Davidson et al 1997, Hershey et al 2000). Overall 1-year disease-free interval was 35% and 2-year disease-free interval 9%. From these data we would not expect a surgical cure with 2 cm margins. The longest disease-free interval for VAS treated with 'wide' surgical resection was that reported by board-certified surgeons, with medians of around 23 months (Cronin et al 1998) and 14 months (Hershey et al 2000).

'Radical' surgical resection

Radical surgical removal, including 5 cm margins laterally around the grossly palpable tumour and two fascial planes on the deep aspect, has also been tried in 100 cats (Kuntz, unpublished data). Clean histological margins were achieved in 97% of these cats, and local tumour recurrence was reported in only 11%. At 1 year, 91% of cats were disease free. This reduced to 86% at 2 years and 74% at 3 years. Six cats treated with chest wall and body resection using a minimum of 3 cm margins did not show any local tumour recurrence for a minimum of 12 months postoperatively (Lidbetter et al 2002). These radical surgeries provide the best disease-free intervals and reported survival times for any treatment. It is possible that these results

could be even better with contrast-enhanced CT or MRI prior to surgery to better define tumour volume and thus enable a more accurate idea of optimal surgical margins.

What is the expected morbidity to the cat with such 'big' surgery? For the 100 cats treated with 5 cm lateral margins and two fascial planes deep, the only major surgical complication was wound dehiscence, associated mainly with interscapular VAS. Chest and body wall resection were well tolerated (Lidbetter et al 2002). These surgeries require significant supportive care, particularly analgesia, and are best performed in a referral centre. Prolonged survival with radical surgical resection is more likely for smaller VAS, detected earlier, and without previous attempts at removal. In some patients with large tumours where primary closure may be an issue, skin-stretching techniques have been used prior to surgery.

However, not all cats will have a positive outcome with surgical resection with clean margins. Cats with point mutations of their *p53* genomic sequence (allelic deletion of *p53*) had rapid tumour recurrence and a reduced overall survival, and attaining clean surgical margins in these cats did not predict a positive outcome. Cats without this allelic loss may have local tumour control when treated with surgical resection with clean margins (Banerji & Kanjilal 2006).

Marginal excision

Removal of VAS with incomplete resection(s) impacts negatively on disease recurrence and survival (Banerji & Kanjilal 2006, Davidson et al 1997, Hershey et al 2000). VAS treated with marginal excision recurs faster than those treated with radical excision or marginal excision and radiotherapy, with a median disease-free interval rarely more than 1 year (Hershey et al 2000). The median time to first recurrence following marginal excision is 79 days, compared to 325 and 419 days for wide resection or radical surgery (Hershey et al 2000).

As mentioned above, radical surgery provides the longest survival times and disease-free intervals for feline VAS. However, not every client will agree to this kind of surgery, and it may not be justifiable for advanced VAS. Radiation therapy may also not be available or affordable. It is a palliative option to treat cats in these settings by marginal excisions for each recurrent VAS, as long as the client is aware of the continued increased risk of local recurrence, reduced disease-free interval and reduced overall survival time (Davidson et al 1997).

Multimodal therapy

A multimodal approach using marginal excision, adjuvant radiation (with at least a 3 cm wide field of radiation around gross tumour) and doxorubicin chemotherapy has been reported. The median disease-free interval for 29 cats was 15.4 months, with a range of 2.4–44.9 months. This median disease-free interval was superior to that attained for 42 cats treated with marginal excision and radiotherapy, without the addition of chemotherapy (5.7 months, range 1–50.8 months). However, survival for both groups was not statistically different (median 25.7 months when both groups combined) (Hahn et al 2007).

The outcome for postoperative radiation therapy (about 40% local tumour recurrence, median 405 days after surgery) is similar to preoperative radiation therapy (40–45% local tumour recurrence, median 398–584 days after surgery) (Cronin et al 1998, Kobayashi et al 2002). Radiation fields for these cases typically included a minimum 3 cm around gross tumour or surgical scar. Some tumour recurrences occurred outside the radiation field (geographic miss), but most recurred within the field (indicating the need for more aggressive surgical and/or radiation protocols).

Chemotherapy

Partial and complete responses to doxorubicin (±cyclophosphamide) have been reported in about 40–50% of cats with gross VAS, but only for a median duration of 84–125 days (Barber et al 2000, Poirier et al 2002). Cats that respond to chemotherapy survive longer (median 242 days) than those that do not (83 days) (Barber et al 2000). The overall benefit of chemotherapy for VAS is debatable and the best option for these patients remains radical surgical excision.

Immunotherapy

The effect of local immunotherapy, using recombinant poxviruses expressing interleukin-2, in conjunction with surgery and iridium-based radiotherapy, was explored by Jourdier et al (2003). They were able to demonstrate a reduction in the percentage of cats having tumour recurrence in the treated over non-treated group. Interferons (IFNs) are also currently under investigation in the multimodality approach to management of feline sarcomas (Hampel et al 2007).

It is up to the client, the general practitioner, the radiation oncologist, the medical oncologist and the specialist surgeon to discuss the potential risks versus benefits of each treatment option, for each individual cat. The optimal treatment needs to be tailored to the individual cat, the surgeon's capability and the client's expectations.

Future directions

Over the last 10 years much has been learnt about injection sarcomas in cats and the very unique nature of this tumour. There is still much to learn but, as always, prevention is better than cure, and a number of valuable lessons if applied to our feline patients may help to reduce the incidence of this devastating tumour. It has a significant impact on the cat owner, not only because of its aggressive nature, but also because it is associated with responsible pet ownership, i.e. regular vaccination against disease. Consequently, many clients will blame themselves for being too conscientious. It is also disturbing for the veterinary surgeon that has been administering what has been believed to be the best in preventative care for many devastating feline diseases (e.g. FeLV) or conforming to the legal requirements for vaccination against rabies.

The way forward is multifactorial and involves the collaboration of veterinary surgeons, pharmaceutical companies and clients. At the present time, although we do not have all the answers, a number of recommendations should be implemented.

1. Adopt the VAFSTF recommendations concerning sites for vaccination, so that if tumours do develop, surgical treatment is as straightforward as possible (it is better to lose a limb than a life).
2. Refer early to a specialist surgeon/oncologist.
3. Consider the use of non-adjuvanted vaccines and frequency of vaccination dependent on the licence and legal requirement for vaccination.

4. Remember these are injection-associated tumours so minimize subcutaneous injections in feline patients and endeavour to give in regions amenable to surgical excision in the event of tumour formation.
5. This tumour can be beaten!

Feline STS that are not injection associated have similar prognosis to their canine counterparts and should be managed in the same manner. These are the sarcomas that arise in areas where injections would not have been administered such as the extremities, head and neck.

Cutaneous haemangiosarcoma (HSA)

In cats, cutaneous and subcutaneous HSA are uncommon and tend to occur in older cats as single lesions, usually in poorly pigmented areas. Predilection sites include the skin of the head, pinnae, ventral abdomen and inguinal areas. Despite surgical resection, local tumour recurrence occurred in 50% of cases in one retrospective study (Johannes et al 2007). Local recurrence was found to be more likely with subcutaneous tumours as it was more difficult to obtain adequate surgical margins.

HSA located on the ventral abdomen are particularly aggressive and these patients often present in disseminated intravascular coagulation (DIC). Management can be difficult as surgical excision may not be possible and morbidity due to DIC can be high.

Response to chemotherapy (doxorubicin) is anecdotal. Incompletely resected HSA is amenable to radiotherapy as with canine tumours, but, as with the canine counterpart, deeply invasive subcutaneous tumours are more likely to metastasize. In cats, cutaneous and subcutaneous HSA is seen more frequently than visceral disease.

Lymphangiosarcoma

As in dogs, this is a rare tumour. Clinical presentation, treatment and prognosis are similar to canine. Anecdotally, aggressive lymphangiosarcomas have been seen on the ventral abdomen where prognosis is poor due to the difficulty in obtaining clean margins.

Synovial cell sarcoma

This too is a rare tumour in cats, with few reports in the veterinary literature. As with dogs, limb amputation is recommended for cats that have no evidence of metastatic disease.

Histiocytic sarcoma (HS)

Histiocytic disease in cats is less common than in dogs but two different histiocytic disease complexes have been recognized (Moore & Affolter 2005), progressive histiocytosis and HS/MH. (For a discussion of feline progressive histiocytosis, see Chapter 18.)

HS (as defined in the section on canine HS) has been recognized in cats. These are primarily located in the subcutaneous tissues of the extremities and ventral abdomen. HS has also been identified in the spleen. It appears to resemble canine HS and treatment options are the same, although the role of radiotherapy and chemotherapy has not been identified.

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Tumours of the skeletal system

CANINE BONE TUMOURS

The current incidence of bone tumours in dogs is in the order of 7.9/100 000 (Dorn 1976, Dorn et al 1968). Of these, 98% are malignant (Brodey & Riser 1969). Tumours of the bone can be divided into three groups – primary bone tumours, tumours metastatic to bone and tumours that have invaded into bone.

Primary bone tumours

By far the most common tumour of bone is osteosarcoma (OSA). This malignant tumour accounts for approximately 85% of all primary bone tumours (Brodey & Riser 1969). Other tumours include other sarcomas, e.g. chondrosarcoma (CSA), fibrosarcoma (FSA) and haemangiosarcoma (HSA), which account for approximately 5–10% of all bone tumours. Other rare tumours include lymphosarcoma, plasma cell tumours, osteomas, chondromas and other sarcomas, e.g. liposarcoma (Brodey & Riser 1969, Nielsen 1976).

Osteosarcoma

OSA is a malignant mesenchymal tumour of primitive bone cells. These cells produce osteoid (matrix), differentiating them from other sarcomas of bone. A histological diagnosis requires a large enough biopsy so that OSA is not confused with reactive bone, osteomyelitis, CSA, HSA or FSA. OSA is locally aggressive, causing lysis and/or production of bone and soft tissue swelling, and may cause pathological fractures.

OSA arises in both the appendicular and axial skeleton. Large breed dogs with increased height are considered to be at greater risk than small breed dogs (Brodey & Riser 1969, Ru et al 1998). In fact, 90% of all OSA arise in dogs that weigh greater than 20 kg (Brodey & Riser 1969). The majority of canine OSA develop spontaneously but they have also been associated with previous radiation therapy, as a result of fractures, placement of metal implants and as a consequence of bone infarcts (Withrow & Vail 2007).

The appendicular skeleton accounts for approximately 75% of cases, with the metaphyseal region of bone the most common location and tumours arising more frequently in the fore than the hind leg (2:1) (Knecht & Priester 1978). The distal radius/ulna is the most common location, accounting for 40% of all OSA. The phrase 'away from the elbow, towards the knee' has been coined to describe the most frequently affected sites on the long bones; however, it is important to remember that this is an indication only and OSA are not restricted to these locations. The distal radius and proximal humerus are the most common locations ('away from the elbow') (Knecht & Priester 1978). In the hind leg, distribution appears fairly even between distal femur, distal tibia and proximal tibia, with proximal femur less common (Brodey & Riser 1969). It is very unusual for primary OSA to cross a joint surface, or to occur distal to the antebrachiocarpal or tarsocrural joints, or to occur at the proximal radius or distal humerus (Gamblin et al 1995, Liptak et al 2004a).

OSA of the axial skeleton, although less common than their appendicular counterparts, are an important cancer of dogs. Approximately 50% of axial OSA occur in bones of the skull, those affecting the mandible and maxilla being most common. The rib accounts for 25% of axial skeleton OSA. Less frequently seen are those of the cranium, scapula, vertebrae, pelvis and sternum (Heyman et al 1992). The biological behaviour of rib and scapular OSA is more compatible with the appendicular rather than the axial skeleton (Kirpensteijn et al 1994, Matthiesen et al 1992, Pirkey-Ehrhart et al 1995). In the smaller breed dogs (<15 kg) the incidence of OSA, as a percentage of all skeletal neoplasms, is 45% as opposed to 85% seen in the large breeds (Cooley & Waters 1997). Axial and appendicular skeleton are almost equally represented in small breed dogs, with the femur and tibia as the most common appendicular sites (Kistler 1981). Metastatic bone tumours account for about 25% of all bone tumours in small dogs, compared to <5% in large dogs (Cooley & Waters 1997). Finally, extraskeletal OSA is an uncommon and extremely aggressive malignancy (Kuntz et al 1998, Langenbach et al 1998).

Appendicular osteosarcoma

Signalment

- *Age*: 7.5 years median age with a second peak at 1.5 years (Misdorp & Hart 1979).
- *Breed*: Large breeds with Rottweilers, Great Danes, St Bernards, Irish Wolfhounds and Greyhounds over-represented (Brodey & Riser 1969, Rosenberger et al 2007). Increasing age (Rosenberger et al 2007), height and weight correlate with increased risk (Ru et al 1998).
- *Sex*: one large study showed an M:F ratio of 1:1 (unpublished data CSU-ACC OS database). Neutered dogs have a higher risk than intact animals (Cooley et al 2002, Ru et al 1998).

Clinical signs

These patients usually present with signs of intermittent lameness that initially is responsive to non-steroidal anti-inflammatory drugs (NSAIDs). In some instances the patient may become acutely lame after running, or the client will notice a hard swelling on the leg. The clinical signs of pulmonary metastatic disease from a primary bone tumour are most commonly inappetence and malaise, and respiratory signs are uncommon. Hypertrophic osteopathy may develop in dogs with pulmonary metastasis.

Physical examination

In many cases the patient will have a hard swelling on the affected leg. Depending on the individual, this may or may not appear to be painful, and in some cases there may be significant soft tissue swelling. The degree of lameness is extremely variable at presentation, from toe-touching lame to non-weight bearing, and seems to have very little correlation with the radiographic signs. Acute lameness with a pathological fracture accounts for <3% of all fractures (Boulay at al 1987).

Pain may be elicited on deep bone palpation in early cases, where soft tissue swelling is not obvious.

Diagnostic work-up

Radiography

A history of unexplained lameness or the presence of a firm mass warrants radiographic assessment (lateral and craniocaudal views) of the affected bone. Features of an aggressive bony lesion may include one or all of the following (see **Figure 21.1A–D**): a loss of fine trabecular detail of the metaphyseal bone due to lysis, discontinuity of the cortex, periosteal new bone formation (Codman's triangle), palisading mineralization perpendicular to the bone shaft ('sunburst effect'), extension of a mass into the adjacent soft tissues, an indistinct transitional zone between tumour and normal bone, inappropriate areas of sclerosis, or pathological fracture. OSA does not cross the articular cartilage, although tumour may extend into soft tissues and to adjacent bones. Primary lesions usually remain monostotic. CT scans, when available, give a more accurate evaluation of the extent of affected bone.

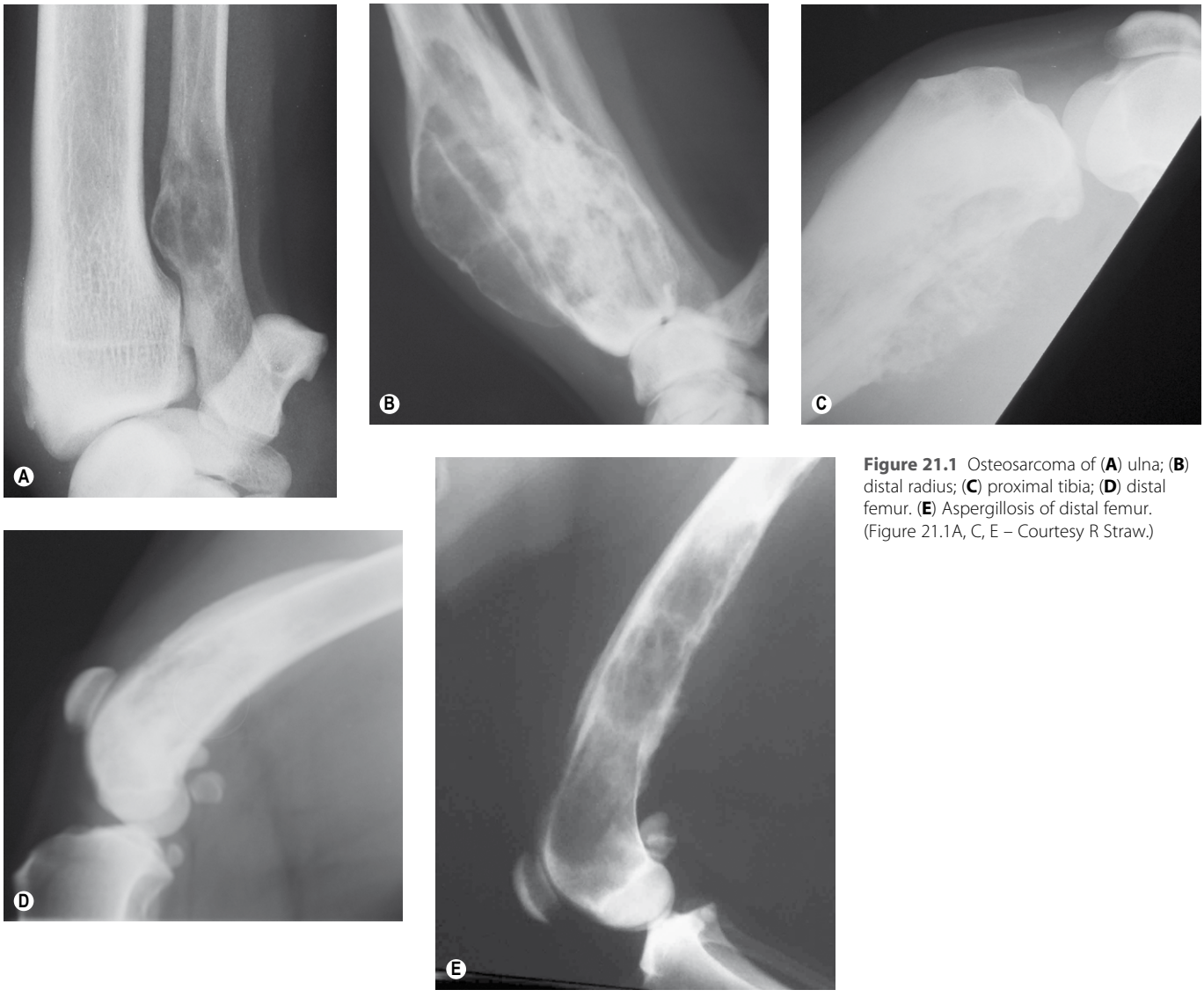

Figure 21.1 Osteosarcoma of (**A**) ulna; (**B**) distal radius; (**C**) proximal tibia; (**D**) distal femur. (**E**) Aspergillosis of distal femur. (Figure 21.1A, C, E – Courtesy R Straw.)

The differential diagnosis for a radiographic aggressive bony lesion includes bone tumour (primary or metastatic), infection (**Figure 21.1E**) (fungal or bacterial), and (rarely) bone cysts.

Bacterial osteomyelitis is suspected on the basis of history (as contamination from surgery or trauma is more common than haematogenous spread). Mycotic osteomyelitis is a major differential diagnosis in countries where fungal diseases are common as they can be monostotic with preference for metaphyseal lesions and spread is haematogenous; however, most mycotic diseases are polyostotic and associated with pulmonary infiltrates and thoracic lymphadenopathy. Travel history and the signalment of the patient may be indicative of a fungal infection.

Clinical staging

Haematology, biochemistry and urinalysis are standard. Routine blood work is often normal; however, there may be an elevation in alkaline phosphatase (ALKP), which may be of value as a prognostic indicator (see below).

Thoracic radiographs (preferably three views) should be taken. Less than 10% of dogs with OSA have visible pulmonary metastases at the time of initial examination; however, if present, the prognosis is poor (Brodey 1965). Bone survey radiographs were more useful in the detection of metastatic lesions (6.4%) than were chest radiographs (4%) in one study of 171 dogs (Straw et al 1989a).

Advanced imaging is useful for the diagnosis of occult metastatic bone disease, and more sensitive detection of pulmonary metastatic disease (CT, MRI, nuclear and CT/PET). CT allows better evaluation of cortical erosion, fractures and internal characteristics such as ossification and calcification (**Figure 21.2**). It may also be more useful in detecting pulmonary metastatic disease compared to thoracic radiographs. The increased availability of CT does mean that metastatic lesions not seen on plain radiographs are being identified. Whilst this inevitably impacts on our discussions with our clients, all the data currently available on survival times have been derived from patients staged with radiographs. Our ability to see these lesions should not stop us treating patients but may make it easier to explain the importance of follow-up chemotherapy to the client.

In addition to the lung, the most common metastatic site is to bone (**Figure 21.3A,B**) and care should be taken to evaluate the patient as much as possible for evidence of bony metastases. Other sites include kidneys (**Figure 21.3C**), spleen, myocardium, lymph nodes (regional and distant), diaphragm, mediastinum, spinal cord, small intestine, gingiva and subcutaneous tissue. A surgical staging system has been devised for human bone sarcomas, and most dogs present with stage IIb disease using this system (Table 21.1).

Bone scintigraphy is useful for diagnosing occult metastatic bone lesions. It is indicated for polyostotic bone disease or bone metastasis. Bone scintigraphy cannot differentiate benign from malignant or accurately determine the extent of tumour. It has no value for pulmonary metastasis. A number of studies have looked at the incidence of occult bone metastases using scintigraphy and, depending on the study, between 4 and 28% of patients with OSA may have bony metastases (Berg et al 1990, Hahn et al 1990, Janowski et al 2003, Lamb 1987, Parchman et al 1989). However, the limited accessibility to scintigraphy means that most patients are treated based on plain radiographs. In those patients where the 'primary' appears to be located in an atypical location for OSA, scintigraphy, if available, should be considered.

Bone biopsy

Histopathology is required for definitive diagnosis of a bone tumour. Presurgical biopsy techniques include closed (Jamshidi needle), open, or limited open (Michele trephine). The skin incision is made so that the biopsy tract and any potentially seeded tumour cells can be completely removed at the time of definitive surgery. Care is used to avoid major nerves, vessels and joint spaces.

Jamshidi

A 4-inch, 8–11 G bone biopsy needle is used through a small stab incision in the skin. Two to three biopsies of the centre of the lesion (as determined from radiographs) are taken via the same skin incision (only once the cortex is penetrated). The diagnostic accuracy is 82% for specific tumour type and 92% for differentiating tumour from other causes, and complications are uncommon (Powers et al 1988). Post-biopsy radiographs confirm the position of the biopsy tract. Material for culture and

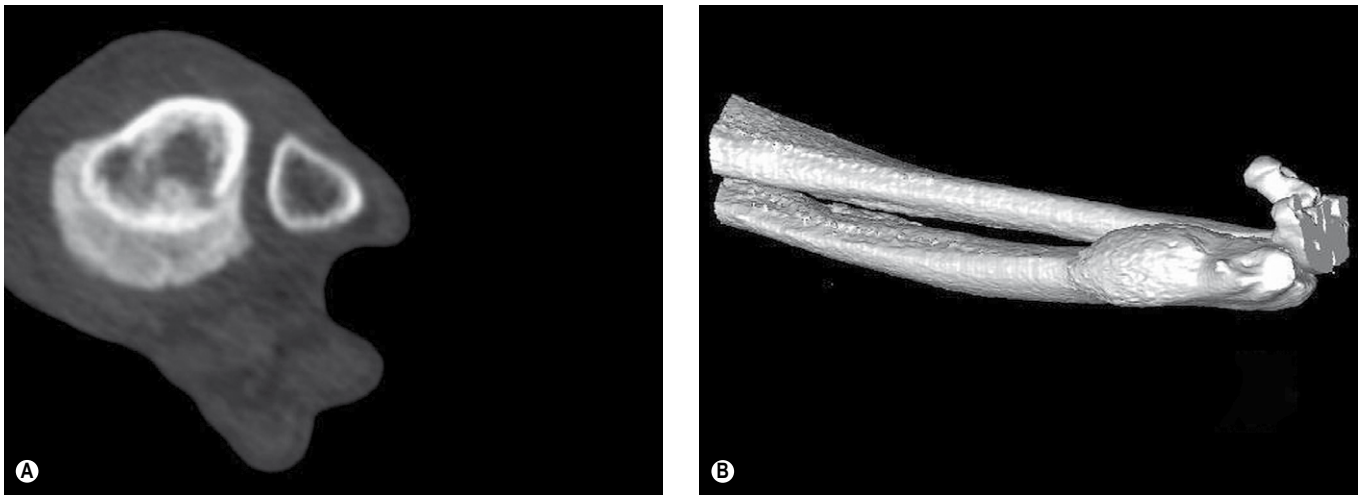

Figure 21.2 (**A**) CT image with (**B**) 3-D reconstruction of osteosarcoma of distal radius.

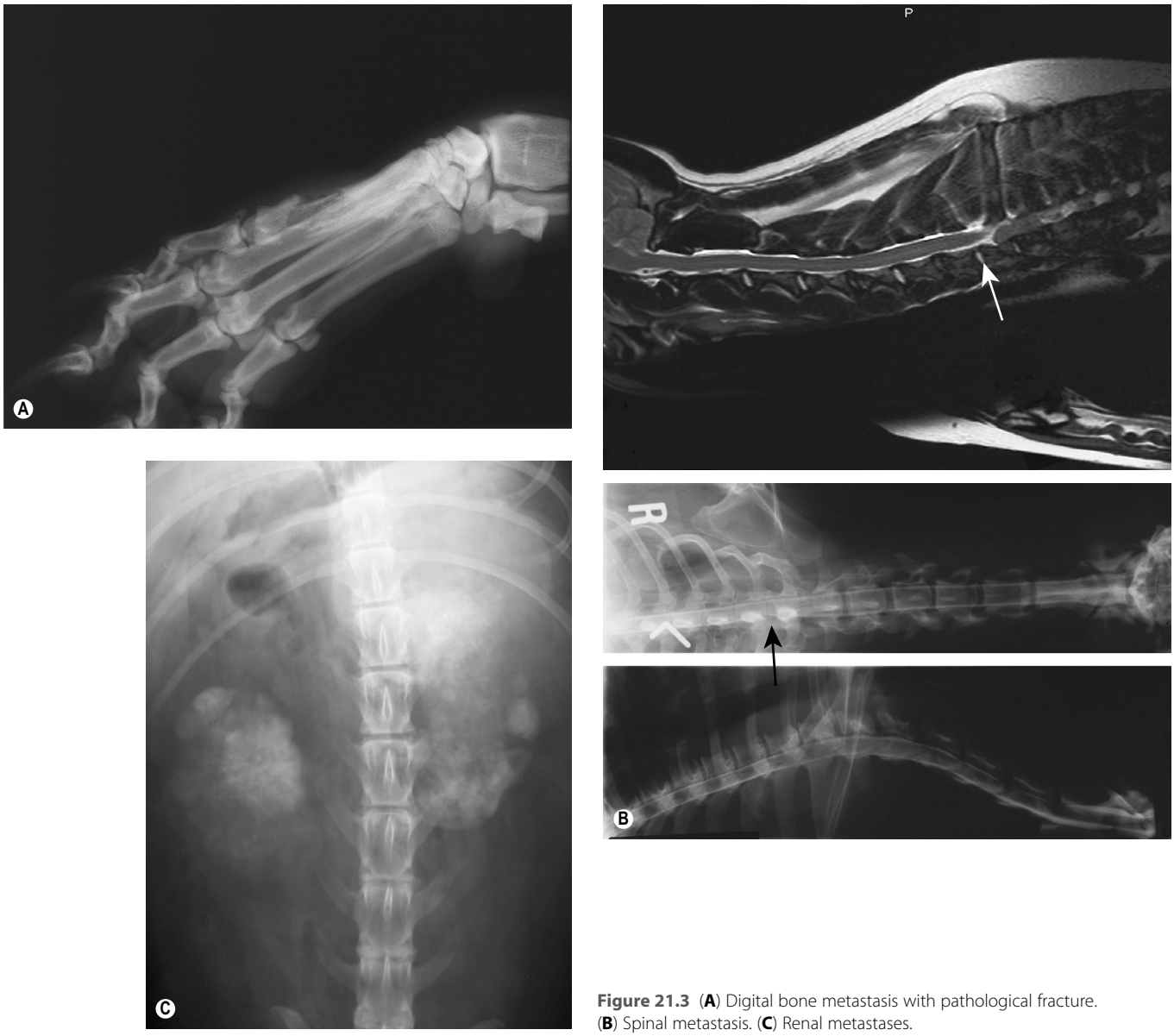

Figure 21.3 (**A**) Digital bone metastasis with pathological fracture. (**B**) Spinal metastasis. (**C**) Renal metastases.

Table 21.1 Surgical staging system for human bone sarcomas*

Stage	Characteristics
I	Low grade without evidence of metastasis
II	High grade without evidence of metastasis
III	Any grade with metastasis
A (T1)	Intracompartmental
B (T2)	Extracompartmental

*Most dogs with osteosarcoma present with stage IIb.

cytology should be taken before fixation in formalin. Fluoroscopy is useful for assisting bone biopsy for axial sites.

Open biopsy

Open biopsy guarantees a large biopsy but with increased risk of operative complications (haematoma, infection, dehiscence, tumour seeding, and pathological fracture).

Limited open (Michele)

This has a diagnostic accuracy of 94% but an increased risk of pathological fracture (Wykes et al 1985).

FNA cytology

Aspiration of the intramedullary region is performed through areas of cortical destruction (can be ultrasound guided). In dogs, ultrasound-guided needle aspirations of aggressive appendicular bone lesions indicated sarcoma with a sensitivity of 97% and a specificity of 100% in 32 of 36 cases. When a diagnosis of sarcoma was made on cytology (**Figure 21.4**), ALKP staining indicated OSA, with a sensitivity of 100% (Britt et al 2007).

- *Advantages*: can be done without general anaesthesia; quicker results; tissue-core biopsy can be performed if FNA is unsuccessful.
- *Disadvantages*: multiple aspirates are often required for a definitive diagnosis, and excessive blood contamination can interfere with cytological evaluation, particularly in the presence of low cellularity, and

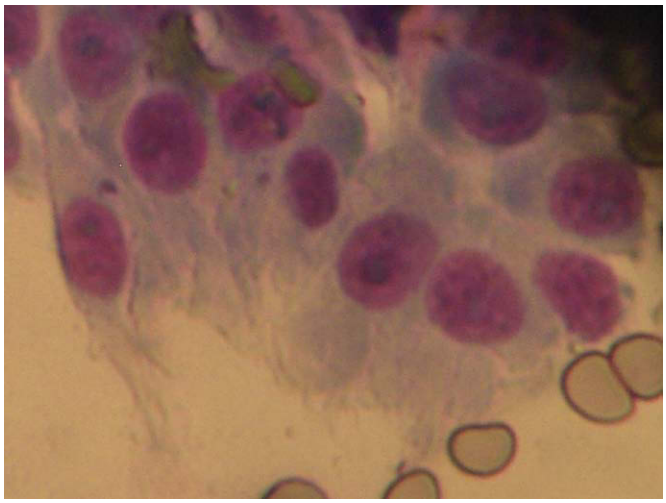

Figure 21.4 Fine needle aspirate of appendicular osteosarcoma.

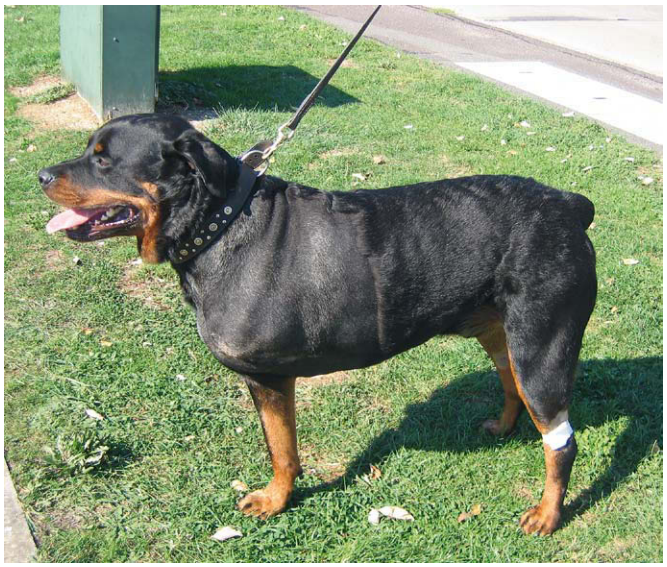

Figure 21.5 Rottweiler post forelimb amputation.

cortical bone destruction must be present. Cytology is limited to tumour group and cannot accurately differentiate between the various members of the sarcoma family.

Excisional (postoperative) biopsy

This should always be done to confirm the preoperative incisional biopsy. If a presumptive diagnosis of OSA is made, and limb salvage is not considered an option, amputation can be performed and the tumour then sent for histopathology. A presumptive diagnosis of OSA can be made based on signalment, history, location, physical examination and radiographic features (especially when there is little possibility of fungal or bacterial infection).

Prognostic factors

Medullary OSA is classified according to the predominant mesenchymal component: osteoblastic, chondroblastic, fibroblastic, telangiectatic (vascular) or poorly differentiated. These histological subtypes of OSA in dogs have similar biological behaviour and prognosis. However, the histological grade (based on microscopic features) may be predictive for systemic behaviour (metastasis) (Kirpensteijn et al 2002, Loukopoulos & Robinson 2007). Tumour vascularity may also be prognostic (Coomber et al 1998).

The presence of visible metastatic disease on thoracic radiographs is a negative prognostic indicator (Boston et al 2006), as is the rare finding of a positive lymph node (Hillers et al 2005). Increased serum ALKP (bone, liver or total isoenzymes) has been shown to be a negative prognostic factor (Ehrhart et al 1998, Garzotto et al 2000). Dogs with high bone ALKP before surgery had shorter survival and disease-free intervals. Failure of bone ALKP to decrease after surgery was correlated with shorter survival and disease-free intervals (Ehrhart et al 1998). Dogs with normal pre-treatment total and bone ALKP survived longer than those with increased pre-treatment values (Garzotto et al 2000). In a multi-institutional study of 162 dogs with appendicular OSA treated with amputation alone, dogs younger than 5 years had a worse survival than older dogs (Spodnick et al 1992). Additional studies have related large tumour size (Misdorp & Hart 1979) and humeral location (Bergman et al 1996) to poor outcome.

Clinical stage is prognostic. In a paper of 90 dogs with stage III OSA, the median survival time (MST) was 76 days. Dogs treated palliatively with radiotherapy and chemotherapy lived longer (130 days) than dogs in all other treatment groups. Dogs treated with surgery alone lived 3 days, compared to dogs treated with surgery and chemotherapy (78 days). Dogs with bone metastases had a longer survival time than dogs with soft tissue metastases (Boston et al 2006).

Location of the primary may be influential in determining outcome. For example, in one study looking at OSA of the ulna, 12 cases were examined with a distribution of 1 : 1 metaphyseal to diaphyseal. All were treated with amputation or ulnectomy and adjuvant chemotherapy, and the median survival time was 8.5 months (Straw et al 1991a). OSA distal to the antebrachiocarpal or tarsocrural joints may carry a better prognosis as in one small study (nine cases) the median survival time was 466 days (Gamblin et al 1995).

Scapular OSA has an MST similar to appendicular OSA when treated with surgery and chemotherapy. In many cases a partial scapulectomy can be performed and up to 90% of the scapula can be excised with good to excellent function. Metastatic potential is high and adjuvant chemotherapy (carboplatin) is recommended in these patients (Kirpensteijn et al 1994).

Treatment

The approach to treatment should consider 'life' and 'limb'.

Limb

Amputation is a pain-relieving procedure, and is considered by many to be the best way to relieve the pain caused by the primary tumour. Amputation alone is considered palliative, although the prognosis is better than no treatment (Spodnick et al 1992, Zachos et al 1999). Amputation with or without adjuvant therapy is the standard treatment for appendicular OSA. There are few contraindications to amputation (see **Figure 21.5**). Concurrent osteoarthritis may progress more rapidly following amputation, although this may be managed medically and most dogs compensate rapidly. Forequarter

(including scapula) amputation is required for thoracic limb lesions. Coxofemoral disarticulation is performed for distal pelvic limb lesions and disarticulation combined with en bloc acetabulectomy is used for proximal femoral lesions. Most clients (42/44) were satisfied with the outcome of amputation, and surprised at the rapidity of their dog's adaptation. No significant association between adaptation with weight, age or thoracic or pelvic limb amputation was found (Kirpensteijn et al 1999).

Radiotherapy

This is a palliative treatment for primary and metastatic bone pain. Response and duration of response depend on the size of the lesion, radiation protocol, and whether or not chemotherapy is used in conjunction with radiotherapy. Response (improvement in limb function) occurs in 75–92%, for variable durations (Green et al 2002, Ramirez et al 1999). Reported response duration ranges from 17 to 288 days (median 130 days). In the authors' experience, dogs with lesions in the proximal humerus do not respond as well as other locations. Typical protocols are 8–9 Gy once weekly for three or four treatments. Radiation should be considered in all patients where surgery is not an option.

Limb-spare

The primary OSA is removed and the limb remains functional by the implantation of another material (e.g. bone autograft, bone allograft, steel prosthesis; see **Figure 21.6**) or by distraction osteogenesis (Withrow & Vail 2007). Intraoperative radiotherapy has been attempted in a few cases (Liptak et al 2004b). Limb sparing may be used where amputation is declined, or dogs have significant pre-existing orthopaedic or neurological disease. It must be stressed that in the vast majority of cases, amputation is the simplest, quickest, cheapest and best method of treating the primary tumour.

For a patient to be suitable for a limb-spare procedure, tumour must be clinically and radiographically confined to the limb and involve <50% of the bone (Withrow & Vail 2007). MRI, CT, nuclear scintigraphy and radiographs may be used to estimate the extent of the tumour (Davis et al 2002, Wallack et al 2002). Pathological fracture is a contraindication due to contamination of soft tissues, although this can be reduced by radiotherapy and neoadjuvant chemotherapy. The most suitable sites are the distal radius and ulna (Withrow & Vail 2007).

Surgeons experienced in limb salvage techniques are not always readily available and only experienced surgeons should perform these techniques.

Chemotherapy (Table 21.2)

Cisplatin or carboplatin alone or in combination with doxorubicin have been shown to significantly improve life span. However, irrespective of the protocol employed, the MST remains in the order of 300–365 days with 2-year survival times at 20–25% (Berg et al 1992, 1997, Bergman et al 1996, Chun et al 2005, Kent et al 2004, Mauldin et al 1988). Currently, the most widely used protocol is single-agent carboplatin and this is our recommended treatment for middle-aged to older dogs with OSA. Three to four cycles every 3 weeks at 300 mg/m^2

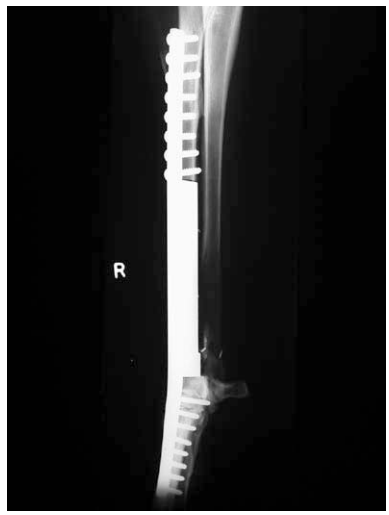

Figure 21.6 Kuntz spacer limb-spare. (Courtesy R Straw.)

Table 21.2 Adjuvant chemotherapy and survival for dogs with OSA where amputation or limb sparing has been performed

Drug	Dose	Number of dogs	Median disease-free interval (days)	One- year survival rate	Median survival time (days)
Carboplatin	300 mg/m^2 IV, 4 cycles at 21-day intervals	48	257	35%	321
Cisplatin	70 mg/m^2 IV, 2 cycles at 21-day intervals	26	177–226	38–43%	262–282
Doxorubicin and carboplatin alternating sequentially	Carboplatin (300 mg/m^2) D1, doxorubicin (30 mg/m^2) D 21, alternating at 3-week intervals for 3 cycles/drug	32	277	48%	320
Doxorubicin and a matrix metalloproteinase inhibitor (BAY 12-9566)	Doxorubicin 30 mg/m^2 every 2 weeks for 5 treatments.	303	Not reported	35%	8 months

See text for references.

have resulted in median survival times of 321 days (Bergman et al 1996). Carboplatin (see Chapter 6) has fewer side effects than cisplatin, does not require diuresis prior to administration and can therefore be given on an outpatient basis. Although it is an expensive drug, the fact that administration is easier means that it is more cost effective than cisplatin.

Combination protocols are generally held to be superior to single-agent protocols (see Chapter 6). However, in the management of OSA there seems to be little benefit to a combination protocol for the majority of patients and when balancing toxicity versus long-term benefit, carboplatin as a single-agent stands up well. Studies alternating doxorubicin and carboplatin or doxorubicin and cisplatin at 3-weekly intervals for three to four cycles/drug did not show any survival benefit over three cycles of carboplatin (median 320 days) (Kent et al 2004, Moore et al 2007). Doxorubicin as a single agent (adjunctive to amputation) every 2 weeks for five cycles resulted in an 8-month MST and a 17% 2-year survival rate in 303 dogs (Moore et al 2007). In younger patients that have a poorer prognosis the authors generally combine doxorubicin and carboplatin but until enough studies are carried out on younger patients the true benefit of this combination remains unknown. Greyhounds show significant myelosuppression with carboplatin that usually results in a reduction of dose to around 250 mg/m^2. Treatment delays because of low neutrophil counts are more common with greyhounds than other breeds and, in the authors' experience, because of regular dose reduction, these patients appear to have an overall poorer prognosis with shorter survival times.

Bisphosphonates These have been shown to decrease metastatic and primary bone pain, improve quality of life and delay progression of bone lesions. They inhibit bone resorption without inhibiting bone mineralization, allowing stabilization of bone mineral density. As nephrotoxicity is the main side effect, renal parameters should be closely monitored.

Bisphosphonates may be of benefit in those patients not amenable to other forms of therapy. Pamidronate with an NSAID alleviated pain for more than 4 months in 28% of 43 dogs, lasting a median of 231 days (Fan et al 2007).

Currently, the availability of alendronate (an oral bisphosphonate) makes dosing easier. This drug appears to be well tolerated.

Expected prognosis based on treatment

- *No treatment*: marked pain due to extensive destruction of bone and surrounding soft tissue. Euthanasia usually elected soon after diagnosis due to pain.
- *Analgesics only*: use of bisphosphonates, NSAIDs, opioids and other analgesics for medical management of the primary tumour still rarely increase survival beyond 3 months.
- *Amputation alone*: MST is 119–175 days with a 12-month survival rate of 11–21% and 24-month survival rate of 0–4%. Death is due to metastatic disease, usually to the lungs (Mauldin et al 1988, Spodnick et al 1992, Straw et al 1991b, Thompson & Fugent 1992).
- *Amputation or limb-sparing and adjuvant chemotherapy*: MST is 262–540 days with a 12-month survival rate of 33–69%. This depends on the chemotherapy protocol, stage of disease, location and signalment (Berg et al 1992, 1997, Bergman et al 1996, Chun et al 2000, 2005, Kent et al 2004, Mauldin et al 1988, Moore et al 2007, Straw et al 1991b, Thompson & Fugent 1992). Most protocols include small numbers of dogs where all factors concerning each individual patient are considered as equal. However, the most important point is that chemotherapy increases the MST for patients with OSA and should be recommended. The other interesting point is that, irrespective of how we combine drugs, the MST still remains in the order of 10–12 months. Interestingly, the MST for dogs that develop an infected limb-spare is increased to 2 years (Devitt et al 1996). Although infection increased morbidity, it has generated an interest in how to stimulate the immune system in conjunction with chemotherapy to improve survival times in these patients.
- *Radiation therapy alone*: response (improvement in limb function) occurs in 75–92%, for variable durations. Response durations of 17–288 days (median 130 days) have been reported (Green et al 2002, Mueller et al 2005, Ramirez et al 1999).
- *Radioactive samarium*: this is a radioactive isotope, which is injected intravenously. In 32 dogs with appendicular tumours, 63% had an improvement in the severity of lameness 2 weeks after administration of the first dose, 25% had no change in the severity of lameness, and 12% had a worsening. Median survival time was 93 days, with 9.4% alive after 1 year (Barnard et al 2007).

Axial osteosarcoma

Axial (cranium, mandible, maxilla, nasal cavity, spine, rib and pelvis) bone tumours may present with other signs. For example, skull or nasal cavity bone tumours may present with a mass on the skull, seizures, sneezing, exophthalmos, pain on opening the mouth, facial deformity, or a nasal discharge. Tumours arising from the rib(s) may present with a palpable rib mass, dyspnoea, pain, or rarely pleural effusion. Vertebral bone tumours may present with spinal pain and/or neurological deficits. Bone tumours of the pelvis cause a pelvic outflow obstruction (tenesmus, stranguria) more commonly than lameness.

The biological behaviour for axial OSA appears to be similar to appendicular OSA (aggressive), with the exception of the mandible and possibly the rest of the calvarium (Hammer et al 1995). Pulmonary metastasis was seen in 11% of canine axial OSA (Heyman et al 1992). The metastatic rate at diagnosis is 27% for rib OSA and 17% for skull OSA (Feeney et al 1982).

In general, the approach to treatment of the axial skeleton is different from that for the appendicular skeleton, and tumour-related death in these patients is usually a consequence of local tumour recurrence (80%) rather than metastatic disease (7%) (Heyman et al 1992). Tumours of the scapula and rib should be treated as appendicular OSA with surgical excision and carboplatin chemotherapy. One of the major problems with OSA of the axial skeleton is the surgeon's ability to completely excise the tumour and that directly translates to location and size of tumour on presentation. Primary OSA of the axial skeleton appears distributed at 27% mandibular, 22% maxillary, 15% vertebral, 14% cranial, 10% ribs,

9% nasal cavity/paranasal sinuses and 6% pelvic (Heyman et al 1992).

A number of reports in the literature give varying overall survival times for patients with axial OSA. The major prognostic indicator appears to be size, with smaller dogs having a much better prognosis than large breed dogs (Dickerson et al 2001).

Mandible

As expected, OSA of the mandible carries the best prognosis of all axial OSA locations with tumour invading local bone but pushing rather than invading adjacent soft tissues. In patients where surgical excision margins have been achieved, further therapy is rarely indicated as 12-month survival rates with partial mandibulectomy alone are about 70% (Straw et al 1996). There is a potential benefit of adjuvant chemotherapy for the 30% of cases that do not survive 12 months with resection of mandibular OSA with clean margins. This subset tends to fail due to metastatic disease within the first 3 months.

In patients where margins have not been achieved due to the size of the tumour, the overall survival rate is reduced; repeat surgery to achieve clean margins is recommended if possible (as long as there is no metastatic disease). Radiotherapy to 'clean-up' incomplete margins can be attempted but as bulky OSA is radioresistant the true benefit of adjuvant radiotherapy is unknown. The authors recommend follow-up chemotherapy in patients with mandibular OSA when the histopathology report indicates a high mitotic rate or for dogs with large tumours (>3 cm) or those with elevated ALKP. The authors would also discuss adjuvant chemotherapy with clients in any large breed dog with mandibular OSA.

Maxilla

Maxillectomy is limited to midline hard palate or the cranial vault. The surgical approach is either intraoral or combined dorsal and ventral approaches. The major cause of death in these patients is local failure so early diagnosis and presurgical CT scans may improve the overall survival time in these patients. As expected, caudally located lesions have a poorer prognosis because they are usually larger on presentation than those located rostrally (Schwarz et al 1991).

The value of adjuvant radiotherapy or chemotherapy in these patients is debatable and depends on tumour size, location and mitotic rate. The overall MST for canine maxillary OSA is 4.6–5 months, with a variety of treatments (Wallace et al 1991).

Calvarium

OSA may push on the brain but rarely invades brain parenchyma. There are three sinuses (one sagittal and two transverse). Ligation of two can result in cerebral oedema and herniation but this is not commonly observed in dogs with tumours because collateral venous drainage develops as a result of chronic compression. Closure with temporal muscle and fascia with no replacement of dura or calvarium is the authors' preference; however, reconstructive techniques with cyanoacrylate cement and artificial dura has been advocated.

Orbital

Long-term survival following complete surgical excision has been reported (Hendrix & Gelatt 2000).

Rib

OSA is the most common rib tumour in dogs (63%) (Pirkey-Ehrhart et al 1995). It tends to occur in younger dogs from 4.5–5.4 years of age (Feeney et al 1982, Heyman et al 1992) and telangiectatic OSA has been associated with the highest rate of metastasis (Hammer et al 1995). The most common site of distant metastasis was lung, found in over 50% of cases at necropsy (Feeney et al 1982). Intrathoracic expansion is common.

Treatment is en bloc excision with chest wall reconstruction; caudal rib tumours may require diaphragmatic advancement and other reconstructive techniques. MST following rib resection with no follow-up chemotherapy was 3 months in one study (Matthiesen et al 1992) and following rib resection and chemotherapy was 240 days (Pirkey-Ehrhart et al 1995).

Vertebrae

OSA is the most common extradural spinal neoplasm (46%). Involvement of multiple vertebrae may occur in up to 25% of cases (Morgan et al 1980). Radiographic appearance is nonspecific and inconsistent. Metastatic potential is not known due to early and catastrophic consequences of the primary lesion. Surgical excision is often impossible. MST following combinations of surgery, chemotherapy and radiation therapy is 135 days, with a range of 15–600 days. Postoperative neurological status had a significant influence on outcome and radiotherapy can be used as a palliative treatment to provide analgesia (Dernell et al 2000).

Pelvis

Hemipelvectomy can be performed (Straw et al 1992). It is important to determine the extent of disease in the sacrum, pubis and soft tissue. The urethra must be protected during pubic osteotomy; 2 cm of the sacrum can be removed laterally if necessary.

In patients not amenable to surgical excision, radiotherapy can be used palliatively for pain. Post surgery adjuvant carboplatin chemotherapy is recommended.

Extraskeletal osteosarcoma

OSA can also rarely occur in extraskeletal sites. Diagnosis is based on the morphological pattern of sarcomatous tissue, production of malignant osteoid or bone, high mitotic index and exclusion of an osseous primary bone lesion. Radiographic evidence of calcification is present in 31% of dogs with extraskeletal OSA (Langenbach et al 1998). Eighty-six per cent of canine extraskeletal OSA are poorly differentiated (Patnaik 1990); 80% feline extraskeletal OSA occur in subcutaneous sites and are probably associated with vaccination.

Eighty per cent of extraskeletal OSA involve visceral organs, with reported sites including mammary, subcutaneous, splenic, intestinal, hepatic, renal, testicular, vaginal, ocular, synovial, meningeal and adrenal tissues (Kuntz et al 1998). Causes include trauma in feline ocular OSA, intramuscular injection, liver OSA with aflatoxin, and heterotrophic ossification such as myositis ossificans. In cats, metaplasia of intraocular fibroblasts or sarcomatous changes of heterotopic bone have been implicated following trauma-associated intraocular FSA, CSA and OSA.

Differential diagnosis includes myositis ossificans or dystrophic calcification associated with tumours or inflammation.

Treatment

Treatment comprises surgery and chemotherapy (e.g. doxorubicin, carboplatin). The extent of surgery did not influence prognosis for dogs with mammary OSA.

Prognosis

Metastasis is present at diagnosis in 57% and at necropsy in 85% of dogs. These tumours show aggressive biological behaviour, with 64% metastasizing to the regional lymph nodes. Adjuvant chemotherapy has been shown to significantly increase survival time. The MST for extraskeletal OSA in dogs with surgery alone was 33 days, with surgery and chemotherapy 146 days (Kuntz et al 1998). Overall the best survival times with surgery alone were recorded for mammary OSA with an MST of 90 days compared to 26 days for soft tissue OSA (Langenbach et al 1998).

The major cause of death is local recurrence for soft tissue OSA and pulmonary metastasis for mammary OSA. Negative prognostic factors include tumour size (>15 cm), the presence of metastatic disease and short history of clinical signs.

Surface osteosarcoma

Juxtacortical or parosteal (<1%)

These OSA are less aggressive (radiographically and biologically) in humans and are associated with a better prognosis (90% 1-year survival rates). In veterinary medicine, cortical lysis is minimal or absent radiographically and lesions are well circumscribed (Banks 1971, Withrow & Doige 1980; **Figure 21.7**). Histologically, lesions contain well-differentiated cartilage, fibrous tissue and bone with sparse sarcoma cells, and can be misdiagnosed as osteoma, chondroma and reactive bone.

Periosteal OSA

Of intermediate grade, these OSA are less aggressive than central OSA but more aggressive than parosteal OSA, with a 70–80% cure rate in humans (Rose et al 2006).

High-grade surface OSA

There is one report of a high-grade surface OSA of the thoracic limb on an 8-year-old dog (Moores et al 2003). There was no bone involvement on radiographs, just increased soft tissue opacity. An aggressive OSA was diagnosed on the basis of early metastatic disease and histopathology. All features were consistent with human high-grade surface OSA. In humans, the 5-year survival time is 46% after surgery, with marginal excision more likely to result in local recurrence, and death resulting from disseminated systemic metastases (Okada et al 1999).

Chondrosarcoma (CSA)

CSA is the second most common primary bone tumour (5–10%) but is uncommon in the appendicular skeleton (Brodey & Riser 1969, Withrow & Vail 2007). It is a malignant, cartilage-producing neoplasm arising de novo within the bone. Most (61%) occur in flat bones (nasal cavity, ribs, pelvis, vertebrae and skull) with other sites including appendicular skeleton, digits, os penis and extraskeletal sites (Popovitch et al 1994). They are usually slow growing and slow to metastasize, although behaviour is related to histological grade (I, II, III) (Sylvestre et al 1992). In humans, the best prognosis is achieved after aggressive surgical resection (Bjornsson et al

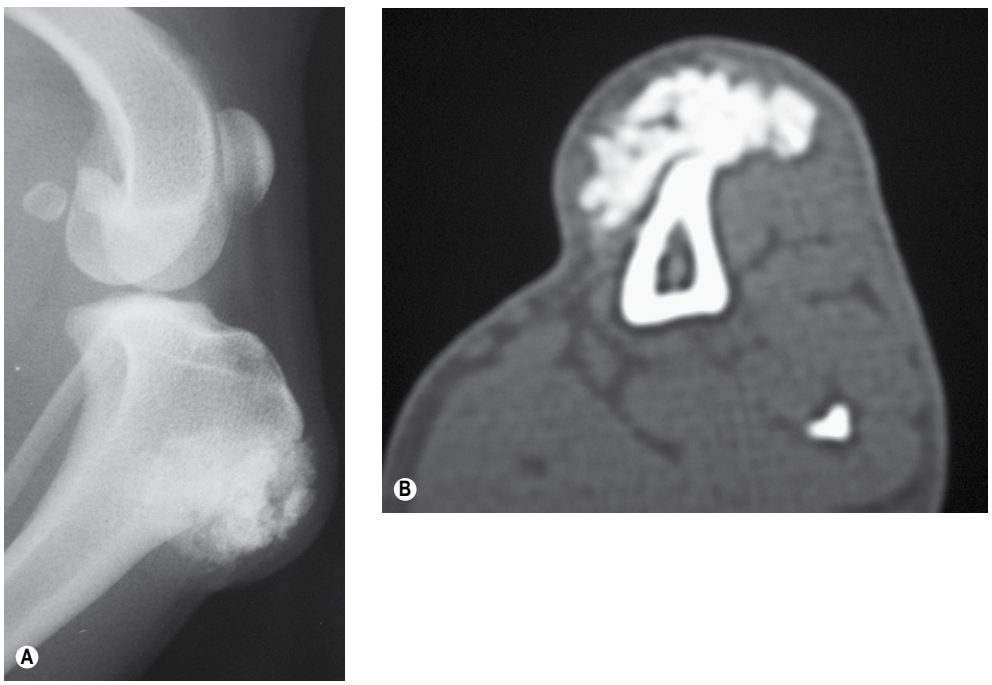

Figure 21.7 (**A**) Radiograph and (**B**) CT scan of parosteal osteosarcoma.

1998) (**Figure 21.8**) and a worse prognosis for recurrence, metastasis and death is found with incomplete excision.

Radiotherapy is reserved for non-resectable lesions, e.g. nasal CSA (**Figure 21.9**). In humans, chemotherapy has not been shown to have a survival benefit even with high-grade CSA.

Tumour location is prognostic, with CSA skull, nasal turbinates and appendicular skeleton having a better prognosis than rib CSA (Sylvestre et al 1992). Histological grade is an important prognostic indicator for CSA (comparing CSA of the same site) (Bjornsson et al 1998). In nasal CSA, MST is 210–580 days and metastasis is very rare (Lana et al 1997, Popovitch et al 1994). In rib CSA, MST is 1080 days with en bloc resection (Pirkey-Ehrhart et al 1995).

Appendicular chondrosarcoma

MST is 201–540 days following amputation (Popovitch et al 1994, Waltman et al 2007). With or without amputation, euthanasia is usually due to metastatic disease (Waltman et al 2007). Metastatic sites include lung, liver and soft tissue. In a study of 31 dogs with non-nasal CSA, 18 dogs treated by wide surgical excision had a mean survival time of 3097 days. Untreated dogs (13) showed a mean survival of 495 days and a median survival of 523 days. The metastatic rate was not statistically different between treated and untreated dogs (Waltman et al 2007).

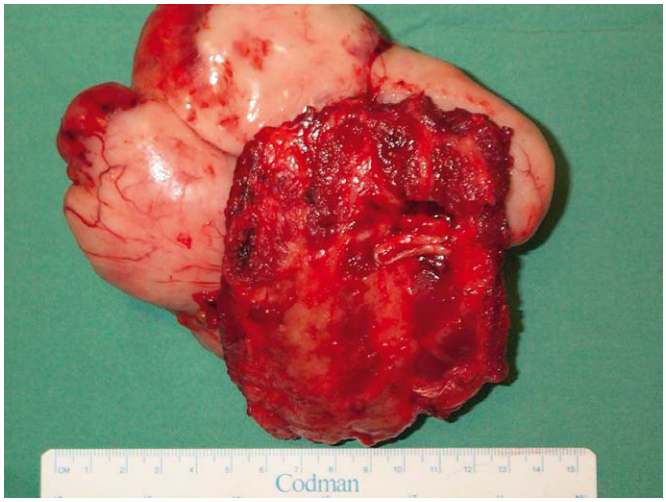

Figure 21.8 Rib chondrosarcoma. (Courtesy R Straw.)

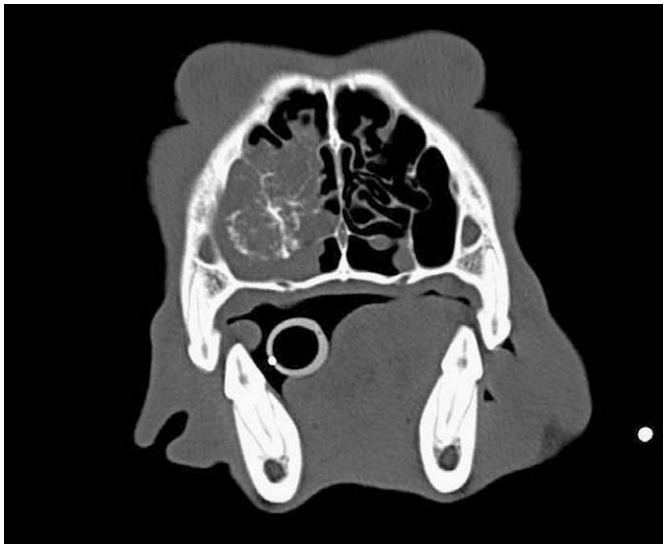

Figure 21.9 Nasal chondrosarcoma in a young Labrador.

Multilobular osteochondrosarcoma (MLO)

MLO is an uncommon bone tumour, arising from the membranous or flat bones of the skull, pelvis or ribs. The common clinical presentation is an obvious, fixed mass protruding from the cranium, mandible or maxilla (Dernell et al 1998). Local tumours tend to be compressive rather than invasive. The characteristic radiographic appearance of an MLO is a faintly mineralized, stippled or coarsely granular tumour with a sharply demarcated appearance and limited lysis of adjacent bone (Dernell et al 1998, Straw et al 1989b).

CT scans show a characteristic rounded, well-defined lesion with fine, granular, non-homogeneous bone opacity (Hatchcock & Newton 2000) (**Figure 21.10**). A CT scan is helpful in planning surgery. Incisional biopsies are taken for definitive diagnosis and grading if possible prior to definitive surgery. Staging should also be performed (particularly thoracic radiographs). In the authors' experience, margins of 0.5–1 cm of grossly normal tissue (if possible) are adequate. Local tumour recurrence is associated with incomplete excision and grade (Dernell et al 1998, Straw et al 1989b).

The metastatic rate is moderate (Lana et al 1997). Removal of local tumour with histologically complete margins is ideal, even in the presence of metastatic disease, as dogs may remain asymptomatic with metastatic lung disease for 1 year or more (Dernell et al 1998). Median time to recurrence has been reported to be from 14 to 26 months. Median time from recurrence to death has been reported to be from 8 to 9.3 months. A low histological grade and complete resection reduce the likelihood of local recurrence and metastasis. Metastatic disease most commonly affects the lungs (90%). Other reported sites include soft tissue, long bone and cerebral cortex, pancreas, kidney, mediastinum and rib (Dernell et al 1998, Straw et al 1989b).

Resection of solitary or a few low-grade metastatic nodules may be beneficial in prolonging survival time. The role of chemotherapy or radiation therapy in prolonging survival time is unclear (Dernell et al 1998). A mean time of 8–11 months has been reported between detection of pulmonary metastasis and death (Dernell et al 1998, Straw et al 1989b). An MST for dogs presenting with metastatic disease and subsequently treated for local disease is 14 months (Dernell et al 1998).

Fibrosarcoma (FSA)

FSA is more common in large breed dogs with the distal radius the most frequently reported location. FSA is the third most

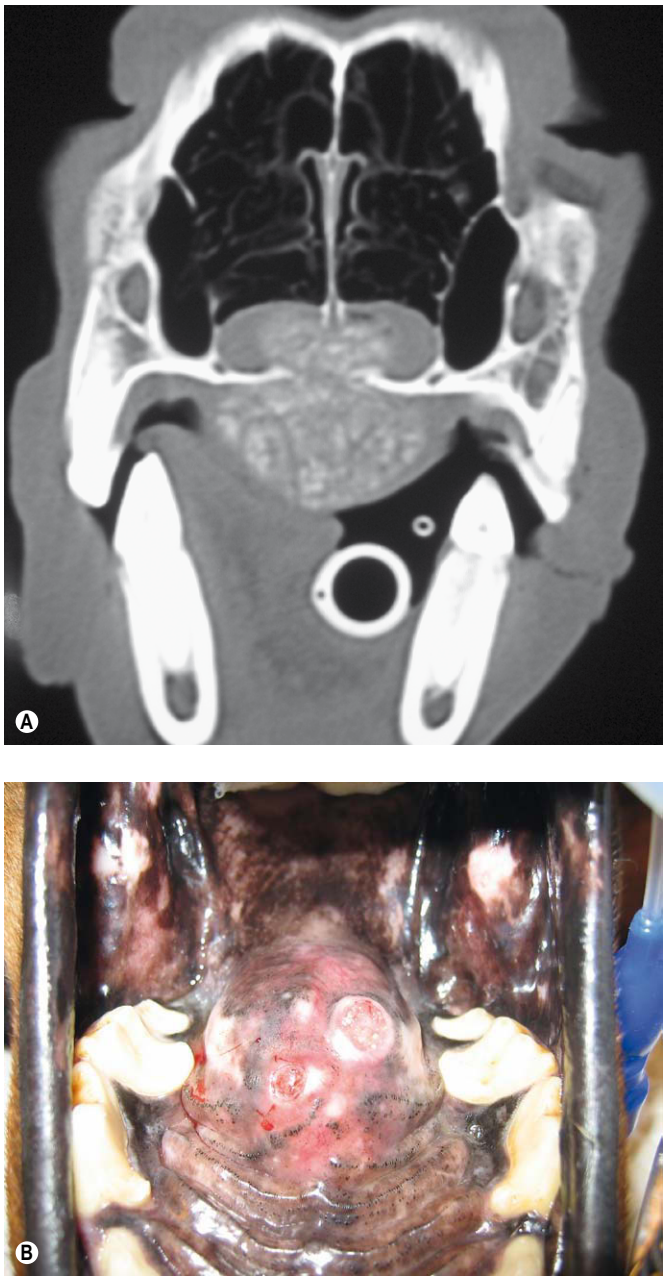

Figure 21.10 Multilobular osteochondrosarcoma of the hard palate of a dog. (**A**) CT scan; (**B**) preoperatively.

common primary bone neoplasm (5–%). FSA may be central (more common, no palpable mass) or parosteal (palpable mass). Appendicular FSA is less malignant than oral FSA and slower to metastasize than appendicular OSA.

Radiographic findings are usually lytic but occasionally can resemble OSA. Histological features are of interwoven bundles of fibroblasts within a collagen matrix producing cancellous and cortical bone but not osteoid. Metastatic sites include heart, pericardium, skin and other bones but usually not lungs (Wesselhoeft Albin et al 1991).

Treatment is surgical and the efficacy of chemotherapy has not been proven. However, in patients with extremely high-grade tumours adjuvant doxorubicin chemotherapy could be considered.

Haemangiosarcoma (HSA)

HSA accounts for 4% of all primary bone tumours. Usual locations are proximal humerus (most common), femur, ribs, vertebrae and scapula. HSA is seen more commonly in middle to older aged dogs, and can affect dogs of any size. There is an equal distribution between axial and appendicular skeletons, and multiple lesions are relatively common. A soft tissue mass accompanies the bony lesion in 50% of cases. Pathological fracture is common.

Measurable metastatic disease is expected within 6 months and the lungs, liver, spleen, heart, skeletal muscle, kidney, brain and other long bones can be affected. Patients may present for a soft tissue swelling that on FNA is blood only and radiographs may show the complete lack of underlying bone due to lysis. Radiographic findings are osteolytic. Ultrasound of the heart and abdominal cavity is recommended.

The prognosis is poor, with a 12-month survival rate <10% even with single bone lesions, due to the high incidence of extraosseous disease (88%) (Ogilvie et al 1996).

Benign bone tumours

Multiple cartilaginous exostoses (MCE)

This is a developmental condition of growing dogs. There are single (osteochondroma) or multiple (osteochondromatosis) forms (Chester 1971). The aetiology may be hereditary in dogs, with possible over-representation of Alaskan Malamute and terriers. The pathogenesis is unknown. Lesions arise from endochondral ossification in areas where new bone is formed on cartilage caps (i.e. metaphysis). Lesions stop growing at skeletal maturity and they usually remain unchanged, mature bony projections. Seventy per cent of lesions are observed at <13 months of age.

Malignant transformation to OSA or CSA has been reported in six dogs with MCE (four with metastases) and two dogs with solitary spinal osteochondromas (Green et al 1999, Owen & Bostock 1971). Common sites are vertebrae, ribs and long bones. No clinical significance is seen unless the lesion interferes with joint movement, compresses vital structures or undergoes malignant transformation. Multiple sites of spinal cord compression are common.

Radiographically MCE appear as bony masses with a fine trabecular pattern on the surface of the affected bone with no evidence of bony lysis or proliferation, the cortex is smooth and can be thin, and the medullary cavity is contiguous with the host bone. Histological diagnosis requires biopsy of the cartilage cap and underlying bony stalk. Differential diagnosis includes disseminated idiopathic skeletal hyperostosis, fluorosis and hypervitaminosis A (very rare in the dog, cannot even be produced experimentally).

Treatment comprises conservative surgical excision if signs do not abate following skeletal maturity. Recommendations include no breeding and advising clients of the risk of late malignant transformation.

Osteoma

Six per cent of all primary bone tumours commonly affect the skull of dogs and cats. They develop from intramembranous bone. Diagnosis is based on clinical signs (usually not painful on palpation), radiographic features (well-circumscribed, dense bony projections) and histological diagnosis (similar to reactive bone).

Treatment is surgical excision, which is usually curative. If the tumour remain static and asymptomatic, consider no treatment, but monitor closely.

Bone cysts

Bone cysts are rare benign lesions in young dogs that present with mild to moderate lameness. Pathological fracture through the cyst can occur. Dobermans and Old English Sheepdogs are predisposed. These cysts are usually located in the metaphysis of long bones but can be diaphyseal and epiphyseal. Aetiology is unknown but trauma to the physis with interference of endochondral ossification is suspected. Rapid resorption and deposition of bone in the metaphysis of growing dogs may result in excessive resorption of a focus of loose fibrous tissue obstructing thin-walled sinusoids and resulting in an accumulation of interstitial fluid.

Radiographic features are of single (or more commonly multilocular), sharply defined, radiolucent defects in the medullary canal of long bones, with cortical thinning with symmetric bone expansion. Histological features are of a thin fibrous wall lined by flat to slightly plump mesothelial or endothelial cells. Treatment consists of meticulous curettage and packing of the defect with an autogenous cancellous bone graft.

Aneurysmal bone cyst

This type of bone cyst comprises spongy multilobulated masses filled with free-flowing blood. These are not true cysts as they are not lined by epithelium. Aetiology is arteriovenous fistulas (malformation), most likely secondary to trauma, or benign bone tumour disrupting normal vasculature and damaging bone mesenchyme, resulting in stabilization of the vascular anomaly and consolidation and maturation of reactive bone. Treatment is en bloc resection and reconstruction or extensive curettage and packing of the resultant defect with an autogenous cancellous bone graft.

Other bone cysts

Subchondral or juxtacortical bone cysts have been described, although communication with synovial membrane is usually demonstrated.

Secondary/metastatic bone tumours

Metastatic bone cancer is most commonly seen with epithelial tumours, e.g. mammary, thyroid, prostate, urinary bladder, squamous cell (**Figure 21.11**), renal, hepatic and in cats pulmonary. Common sites for metastatic bone cancer are lumbar and sacral vertebrae, pelvis and the diaphysis of long bones (nearby blood supply via the nutrient foramen). Multiple skeletal metastases are common despite there often being only one clinical lesion.

Other tumours invasive to bone include any primary soft tissue tumour that may become invasive into underlying bone, e.g. soft tissue sarcomas.

Future directions

In spite of our current level of knowledge, survival times for patients with appendicular OSA have not significantly improved over the last decade and the 1-year 'wall' remains. We continue to evaluate new prognostic indicators and look at better methods for treating our patients. The tumour suppressor gene *p53* has been evaluated as a prognostic indicator and overexpression in appendicular OSA over axial OSA was reported (Sagartz et al 1996); the relevance and application to the clinical patient is as yet unknown.

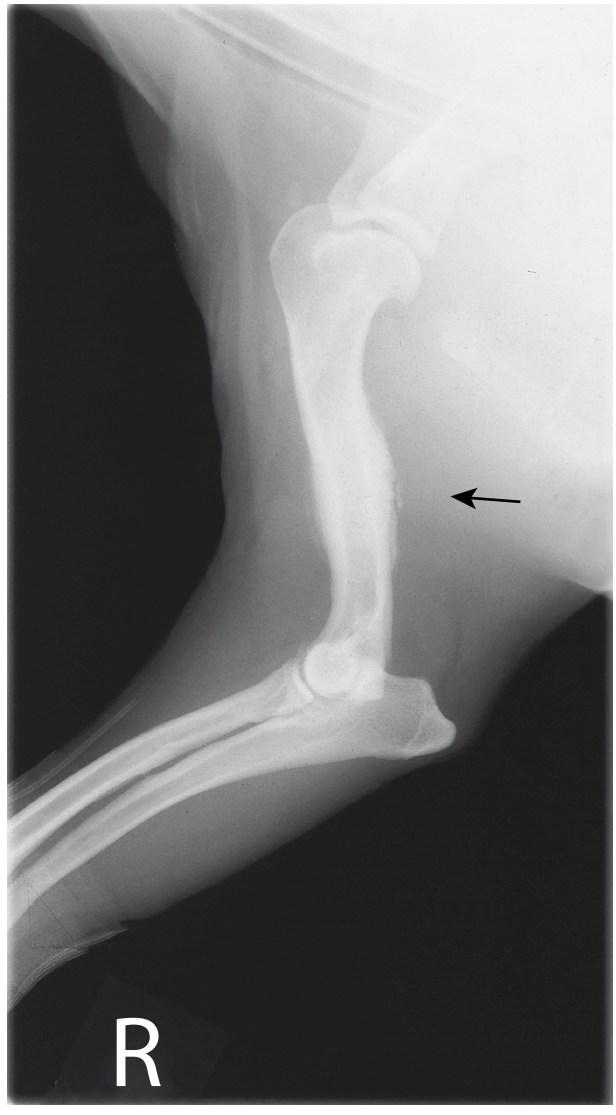

Figure 21.11 Metastatic lesion from oral squamous cell carcinoma.

FELINE BONE TUMOURS

Feline bone tumours are rare (0.5% of all feline tumours). Most are malignant (67–90%), with malignant OSA the most common primary bone tumour (70–80%), then FSA and CSA (Bitetto et al 1987).

Primary bone tumours

Osteosarcoma

Skeletal OSA account for 62% and extraskeletal OSA account for 38% of feline OSA (Quigley & Leedale 1983). Site predilection is debatable, with 55–67% appendicular and 33–44% axial (Bitetto et al 1987, Heldmann et al 2000). Sites include proximal humerus, distal femur and proximal tibia. Feline OSA is more common in the diaphyseal region than metaphyseal and the pelvic limb is more frequently affected. OSA in cats is less aggressive, metastasis is less frequent and occurs later in the course of the disease than in the dog (Bitetto et al 1987).

The mean age of affected animals is 8.5–10.2 years. Axial OSA is usually seen in older animals. No sex predilection has been reported. Clinical signs include lameness and deformity. Radiographic findings are similar to dogs although lesions arising from the periosteal surface and osteolytic lesions are more common in the appendicular skeleton (80%). Intramedullary OSA is more common with axial OSA. Pulmonary metastases are rarely diagnosed. Chondroblastic, fibroblastic, telangiectatic and giant-cell subtypes have been described but are not prognostic (Lui et al 1974, Quigley & Leedale 1983).

Treatment

Amputation alone may be curative in cats with appendicular OSA and chemotherapy is not recommended (Bitetto et al 1987, Turrel & Pool 1982). Combination therapy is recommended for feline axial OSA (Heldmann et al 2000).

Prognosis

Median survival times in appendicular OSA range from 24 to 44 months (Bitetto et al 1987, Turrel & Pool 1982) with only one report (Heldmann et al 2000) of 11.8 months. Axial OSA carries a poorer prognosis due to increased difficulty with local resection and control (Heldmann et al 2000). For cats with extraskeletal OSA, median survival times of 12.7 months are reported.

Multiple cartilaginous exostoses

Single (osteochondroma) or multicentric (osteochondromatosis) forms have been reported (Pool & Carrig 1972). They occur after skeletal maturity in cats with a mean age of 3.2 years (Carpenter et al 1987). There is no breed or sex predisposition, although Siamese cats were originally thought to be predisposed. In contrast to dogs, they do not affect long bones, are rarely symmetrical and are either familial or viral in origin (nearly all cats are feline leukaemia virus (FeLV) positive). Common sites are scapula, mandible and vertebrae. Virally associated MCE are rapidly progressive, with obvious firm, painful swellings that can cause loss of function.

Radiographic findings are of sessile or pedunculated protuberances from bony surfaces, with indistinct borders, loss of smooth contour and evidence of lysis, particularly with malignant transformation. Lesions are composed of hard irregular exostoses with a fibrous and cartilaginous cap. Endochondral ossification extends from the cap for a variable thickness. Surgical resection is difficult, as the cap tends to blend with adjacent tissue. Surgery is indicated for palliation although recurrence is common.

Other primary bone tumours in cats

FSA is the second most common primary bone tumour in the cat followed by CSA and HSA (Heldmann et al 2000). HSA rarely affects the bones of cats. Biological behaviour is largely unknown although metastases have been reported with CSA and HSA (Carpenter et al 1987, Lui et al 1974, Quigley & Leedale 1983).

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Tumours of the haemolymphatic system

CANINE LYMPHOMA

Lymphoma is the most commonly diagnosed malignancy in the dog, with an annual incidence of 114/100 000 dogs (Dobson et al 2002). It is primarily a condition of middle-aged to older dogs (median 8 years). Breeds that are over-represented include Bull Mastiffs, Golden Retrievers and German Shepherds.

Clinical signs

Lymphoma (LSA) is a complex disease and has many manifestations. Eighty per cent of cases present with the classic signs of peripheral lymphadenopathy; however, patients can present with non-specific signs including lethargy, anorexia, polyuria/polydipsia (PU/PD), vomiting, diarrhoea, dyspnoea, haemorrhage, weight loss and neurological signs.

Clinical evaluation

Physical examination

Whilst peripheral lymphadenopathy may be the most common finding, on examination many other abnormalities may be present, including hepatosplenomegaly, abdominal mass, pallor, effusions, etc.

Diagnostic work-up

For all patients a minimum database is required: biochemistry, haematology and urinalysis. Other diagnostic tests depend on the clinical presentation of the patient and include aspirates of enlarged lymph nodes, chest and abdominal radiographs, abdominal ultrasound and biopsies.

Cytology versus biopsy

In the UK, for a dog presenting with peripheral lymphadenopathy the list of differentials is short. Lymphoma is the primary disease to rule out, but other metastatic neoplasia can occasionally present as lymphadenopathy, as can chronic skin disease. When individual nodes are enlarged, especially in the submandibular region, the diagnosis can be more challenging. In other countries with higher incidences of infectious diseases (e.g. *Ehrlichia*) these must be ruled out by appropriate tests. Fine needle aspirate (FNA) is a useful first diagnostic test, whenever possible avoiding the submandibular lymph nodes. However, it is a quick assessment test and for patients with suspected lymphoma further diagnostics are recommended. Flow cytometry allows detailed characterization of the lymphoid population from an FNA and should be utilized when available or practical (see Chapter 4). In the absence of this facility, or when the sample would be too small, then a biopsy is recommended.

The value of a representative biopsy is that this gives the pathologist much more information about the distribution of neoplastic cells throughout the node, which in turn gives the veterinary surgeon more information when discussing treatment and prognosis with the client. Excisional biopsy is best, especially when the nodes are relatively small. In many instances, tru-cut biopsies can be performed accurately, and a number of samples should be taken. Fast-growing lymph nodes may have large areas of necrosis, so to check that you have a representative sample, gently role the slice of tissue on a slide and examine it microscopically; if the majority of the cells are not identifiable, take a further biopsy or change plan and take an excisional biopsy instead.

For patients with lymphoma involving other organs (e.g. primary hepatic, oral, renal), FNA are usually diagnostic because lymphoblasts would not normally be present in these organs. Care should be taken with FNA of the spleen and intestine in the diagnosis of lymphoma. Malignant effusions containing large numbers of lymphoblasts are also sufficiently diagnostic for starting treatment.

For patients presenting with clinical signs related to a paraneoplastic syndrome (PNS), the diagnostic route might not be obvious. Hypercalcaemia is reported in up to 40% of canine patients and many of these do not have peripheral lymphadenopathy. The most efficient approach to the work-up of a dog with hypercalcaemia (especially a young dog) is good quality thoracic radiographs. The anterior mediastinum is the most common location for lymphoma in patients with hypercalcaemia; the second most common location is the bone marrow. Patients that present with possible immune-mediated haemolytic anaemia (IMHA) or thrombocytopenia (ITP) should be thoroughly worked up to rule out underlying lymphoma as both are common lymphoma-associated PNS.

Staging

The recognized staging system for canine lymphoma is based on multicentric disease and is found in Table 22.1. Atypical lymphoma has been classified as stage V; however, it is important to remember that dogs with certain manifestations of lymphoma do have a good prognosis and realistically require a separate classification, e.g. isolated oral lymphoma.

Staging is important as this may influence decisions as to treatment and ultimately prognosis.

Table 22.1 Staging of canine lymphoma

Stage	Characteristics
I	Single node involvement
II	Multiple node involvement on one side of the diaphragm
III	Generalized lymph node involvement
IV	Stages I–III with liver and/or spleen involvement
V	Stages I–IV with bone marrow involvement
	Other presentations of lymphoma
Substage	Substage a – no signs of systematic illness Substage b – signs of systematic illness

Modified with permission from TNM Classification of Tumours in Domestic Animals. World Health Organization, Geneva, 1980, p 46–47.

Prognosis

Multiple factors affect the prognosis in patients with lymphoma (see Table 22.2).

Substage

Patients that are clinically well at the time of diagnosis and starting treatment (substage a) have a better long-term prognosis than those patients that are already ill (substage b). Therefore, treatment should start as soon after diagnosis as possible to prevent a well patient moving from substage a to substage b.

Histological grade of malignancy

A number of grading systems have been described to categorize canine lymphoma and a detailed discussion of these is beyond the goals of this chapter. Anyone interested in pursuing this further is advised to consult a more advanced text.

Most lymphomas are described as high grade (lymphoblastic), intermediate grade or low grade (lymphocytic). As a general rule, lymphoblastic lymphoma responds well to chemotherapy in the early stages but will more rapidly build up resistance, resulting in earlier relapse compared with lymphocytic lymphomas that may be slower to respond but will have longer remission times.

Immunophenotype

This is a valuable tool to distinguish between T- or B-cell origin and currently the information can be obtained from either biopsy or cytological preparations. Typically patients with T-cell lymphomas have a poorer long-term prognosis. This does not mean that patients with T-cell lymphomas will not achieve a complete remission but rather the remission may not be as enduring as patients with B-cell lymphomas. Typically, ~70% of dogs with multicentric lymphoma have disease of B-cell origin.

Paraneoplastic syndromes (PNS)

PNS are common in dogs with lymphoma (Chapter 10), the most common being thrombocytopenia and hypercalcaemia. In some cases the presence of a PNS is a negative prognostic indicator.

Table 22.2 Prognostic indicators and canine lymphoma

Prognostic indicator	Effect	What can the veterinary surgeon do?
Substage	Substage a has a better prognosis than substage b	Diagnose and treat lymphoma patients quickly, whilst still in substage a
Histological grade of malignancy	Lymphoblastic will develop drug resistance early	Obtain as much information as possible – histopathology or flow cytometry
T-cell versus B-cell immunophenotype	T-cell lymphoma develops resistance to standard chemotherapy protocols earlier	Consider treating patients with T-cell lymphoma differently
Paraneoplastic syndromes (PNS)	May reflect immunophenotype of lymphoma, e.g. association of hypercalcaemia and T-cell lymphoma	Treat PNS early
Chemotherapy protocol	Doxorubicin-based protocols have better survival times	Use the best protocols available
Response to therapy	Early development of drug resistance in some patients	Future directions may provide convenient assays to detect drug resistance, e.g. P-glycoprotein expression
Gender?	May be an association with males having poorer survival times, but may really be immunophenotype. In humans males more likely to develop T-cell lymphoma	Immunophenotyping and as above
Age?	Younger patients tend to develop more aggressive disease, lymphoblastic rather than lymphocytic	Treat with first-line drugs, i.e. a doxorubicin-based protocol to obtain the best chance of prolonged remission

Gender

Some studies have suggested that females have a better prognosis than males, although this has not been universally agreed upon.

Age

Younger patients typically have more aggressive disease and therefore shorter survival times.

Response to therapy and the development of multidrug resistance

The development of drug resistance ultimately leads to treatment failure and a 'rule of thumb' is that the first remission is the best remission, and subsequent remissions are in the order of 50% of the first. This means that the first choice drugs should be used in the initial protocol, not kept for salvage later on.

Several mechanisms exist by which tumour cells may acquire resistance and in canine LSA over-expression of P-glycoprotein is one of the major causes leading to the multidrug resistance (MDR) phenotype (Lee et al 1996). Lymphoma cells with the MDR phenotype are resistant to a number of categories of chemotherapeutics, including antimicrotubule drugs (e.g. vincristine), anthracyclines (e.g. doxorubicin) and prednisolone; however, the alkylating agents are not affected by MDR. Drug resistance can be inherent or develop as a consequence of treatment (see Chapter 6 for the mechanisms of drug resistance).

Patients with T-cell lymphomas appear to have more clinical bone marrow suppression that often results in treatment delays or reduced doses that can result in earlier relapse.

Treatment

Chemotherapy

The treatment of choice for the majority of patients with lymphoma is combination chemotherapy. Infrequently, surgery or radiotherapy may be more appropriate.

Chemotherapy protocols

The choice of chemotherapy protocol impacts on overall median survival. A quick survey of the veterinary literature will produce a number of protocols and the choice of which protocol is best for the individual patient depends on a number of factors. These factors include the patient, the concerns of the client, the experience of the veterinary surgeon and the availability of referral, if necessary.

Combination protocols are best

Median survival times (MST) are influenced by the combination of cytotoxics used in the treatment of patients with lymphoma. The more complex the protocol, the better the outcome – for example, using prednisolone alone the MST is 3 months, using COP (cyclophosphamide, vincristine and prednisolone) the MST is 6 months, and using CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) the MST is 12 months (Cotter & Goldstein 1987, Piek et al 1999). As a single agent, doxorubicin gives superior survival times when compared to COP (Carter et al 1987). However, the more complex the protocol, the greater the risk of side effects, and so both the client and the veterinary surgeon must be committed to the management of side effects, should they occur.

What protocol should I use?

The authors use a doxorubicin protocol because it is the incorporation of doxorubicin into protocols for canine LSA that have increased overall survival times (Carter et al 1987, Keller et al 1993, Teske et al 1994). However, when choosing the protocol to use the following factors should also be considered: the experience and setup of the veterinary surgeon, equipment available for handling cytotoxics and adequate 24-hour care should a cancer patient be unwell. In cases where all these factors are not in place, referral for treatment should be discussed and offered to the client.

Oncologists are trained and equipped to deal with the problems that may develop and just as importantly have the experience to individualize treatment depending on age, breed, stage, drug resistance and intolerance. The ability or willingness of the client to travel for specialist care may also impact on the protocol used and the veterinary surgeon should never go beyond their comfort level or equipment as this will inevitably result in poor care for the patient. Cost may also be an issue; the more complex protocols inevitably are financially more expensive and for clients with a limited budget this should be considered at the outset.

Personality of the patient has to be considered in some instances. For dogs that become extremely stressed when at the vets the clients may be unwilling to enter into treatment that involves many weekly visits to the surgery for chemotherapy. In such cases a protocol combining outpatient oral medication (with appropriate monitoring and client information) may be beneficial or a single-agent protocol such as doxorubicin every 3 weeks for five treatments may be suitable (Postorino et al 1989).

Maintenance versus no maintenance?

The debate about the value of a maintenance phase of a chemotherapy protocol is still an area of discussion. The less intense the induction phase, the more valuable is maintenance chemotherapy (e.g. COP). As with any protocol, the question is: 'How long should the induction phase be?' Should it be a set number of weeks, e.g. 25 weeks, or should it be for so many treatments after a complete response has been obtained? Should it be different depending on the stage of disease as patients with advanced disease may require longer or more intense treatment to achieve a complete response or a stable partial response? The simple answer to these questions is that the optimal protocol has not yet been developed and breaching the '1-year wall' for median survival remains the objective.

CHOP protocols

Keller et al (1993) and Matus (1989) both incorporated maintenance phases after induction, with median first remission of approximately 1 year. Garrett et al (2002) compared the response rate, remission, and survival time in dogs with multicentric lymphoma treated with either a standard CHOP protocol (Madison–Wisconsin) with a maintenance phase or a 6-month protocol with no maintenance. Initial response rate in both groups was >90%, and disease-free intervals (DFI) and overall survival times were comparable, demonstrating no survival advantage for patients having an extended maintenance phase. Treatment delays/drug modification was seen in 41% of dogs with 9.4% requiring hospitalization. Median remission was reported at 282 days. Chun et al (2000) reported a median remission of 330 days using a 25-week protocol and Moore et al (2001) reported median remission of 20 weeks using a 15-week protocol. Simon et al (2006) used a 12-week CHOP protocol with no maintenance, which was essentially

the Matus (1989) 6-week induction protocol repeated twice; the median first remission reported was 243 days. The author (SN) typically uses a doxorubicin-based protocol with no maintenance phase (Table 22.3) adapted from the protocol first reported by Matus (1989).

What do I do when the patient comes out of remission?

Everyone hopes that his or her dog will be the one to beat the disease. Unfortunately, this is rarely the case and when relapse occurs, the decision of where to go from here can be difficult. For a patient that has had a long first remission the authors would advise re-induction using the same protocol. If the first remission has not been long, or re-induction does not result in a complete response, then a number of salvage protocols can be considered.

For patients that have not received doxorubicin initially, the authors would recommend single-agent doxorubicin ± an initial dose of L-asparaginase. In cases where doxorubicin has already been used, the authors moved to a modified MOPP (mustargen, vincristine, procarbazine, prednisolone) protocol, substituting CCNU for mustargen and vinblastine for vincristine or CCNU alone (Moore et al 1999) in combination with dactinomycin. Both drugs have been shown as effective rescue agents.

Other rescue protocols include dacarbazine (DTIC) in combination with doxorubicin (Van Vechten et al 1990), DTIC and CCNU (Flory et al 2008), and CCNU and L-asparaginase (Saba et al 2007). Eventually, whatever salvage protocol is used, progressive disease will occur.

Immunophenotyping and chemotherapy

Does it matter if the patient has a T- or a B-cell LSA? That depends on your perspective and whether you intend to do anything about it! If all patients with lymphoma are treated exactly the same, irrespective of stage, location or immunophenotype, the answer may be no; however, in an attempt to increase survival time in patients with T-cell lymphoma the authors routinely give a longer induction. In addition, it has been suggested that dogs with T-cell lymphoma have better outcomes when alkylating agents are included early in the protocol (Morrison-Collister et al 2003).

The authors routinely incorporate CCNU as a first-line drug in the management of canine patients with T-cell lymphoma (Table 22.3) and this has yielded promising results (unpublished communication). The importance of CCNU in improving the outcome for patients with T-cell lymphoma has been shown in studies using this drug for both epitheliotrophic lymphoma and T-cell cutaneous lymphoma. In the former, good responses have been documented (see Chapter 18); in the latter, two studies demonstrated an 80% partial or complete remission after CCNU (Risbon et al 2006, Williams et al 2006).

Does all lymphoma require treatment?

That is an interesting question and the answer is probably no. Indolent lymphoma is seen in older patients that typically present with mild peripheral lymphadenopathy. Biopsy of the nodes should yield a low-grade lymphocytic lymphoma. If the patient is elderly and the disease stable, then close monitoring may be the best option. However, if the characteristics of the lymphoma change, then chemotherapy would be indicated.

Table 22.3 Combination chemotherapy protocol with no maintenance and incorporating CCNU as a first-line drug

Week	Drug	Drug
Week 1	Vincristine 0.7 mg/m^2	Prednisolone 30 mg/m^2 sid
Week 2	Cyclophosphamide 200 mg/m^2	Prednisolone 20 mg/m^2 sid
Week 3	Doxorubicin 30 mg/m^2	Prednisolone 10 mg/m^2 sid
Week 4	Vincristine 0.7 mg/m^2	
Week 5	CCNU 60–70 mg/m^2	
Week 6	Doxorubicin 30 mg/m^2 iv	
Week 7–12	Repeat weeks 1–6 except no prednisolone	
Week 13–15	Repeat weeks 1–3 for B-cell lymphoma and weeks 4–6 for T-cell lymphoma	

A WBC should be taken before each treatment and drugs should only be administered by staff trained in the handling of cytotoxics who are also fully aware of the potential side effects of these drugs and how to treat patients appropriately should problems arise. Monitoring for relapse is advised.

Because these patients are always elderly and therefore have less resilient bone marrow, this particular group of patients may be better on a less aggressive protocol (e.g. COP). Good clinical judgement is essential in managing these patients.

Surgery

Because lymphoma is a systemic disease, surgery other than for obtaining a diagnosis is rarely indicated. Surgical excision of heavily infiltrated spleens may be considered (see Chapter 23), and excision of isolated intestinal lymphoma/gastric lymphoma may facilitate chemotherapy and reduce complications from chemotherapy (Chapter 15). Solitary cutaneous disease may also be treated with surgical excision.

Radiotherapy

Again because of the systemic nature of lymphoma, radiotherapy has a limited but valuable role in the treatment of canine lymphoma. Isolated disease is seen less frequently in the dog than the cat, but it does occur (e.g. oral, rectal), and because lymphoid tissue is extremely sensitive to radiotherapy it can be the treatment of choice.

Radiotherapy has application in the emergency situation, usually for patients in severe respiratory distress due to a large anterior mediastinal lymphoma. It can also be valuable in shrinking individual lymph nodes causing a problem to the patient when other disease is stable.

Half-body radiation in conjunction with chemotherapy has also been used in the management of canine patients (Rassnick et al 2007, Williams et al 2004). In one study, patients with stage II–V disease were started on a CHOP protocol and then given half-body radiation 2 × 4 Gy fractions to the cranial half of the body and 1 month later the same dose to the caudal half of the body. A median remission time of 486 days was reported; overall treatment was well tolerated (Williams et al 2004).

Other approaches

Bone marrow transplantation (BMT)

The tolerance of bone marrow to cytotoxic drugs and radiation is a significant limitation in permitting dose escalation of drugs/radiation known to be effective against lymphoma and other cancers. In the early days of BMT development for human patients, dogs were used to develop the technique and therapeutic model, proving the principle when spontaneous lymphoma in the dog was treated with autologous BMT (e.g. Deeg et al 1985).

Recently, Frimberger et al (2006) reported on the combination of chemotherapy with dose escalation and autologous BMT in the management of LSA. They found that dogs receiving the highest dose of cyclophosphamide (500 mg/m^2, MST 139 weeks) when supported by BMT had longer survival times compared to dogs on lower doses (300 mg/m^2, MST 43 weeks and 400 mg/m^2, MST 68 weeks) and BMT.

Leukaemia and related disorders

What is leukaemia?

Leukaemia is neoplastic disease involving one or more cell types of haemopoietic origin; the primary site of disease is the bone marrow.

Definitions:

- *Aleukaemic leukaemia*: neoplastic cells are absent from the bloodstream but are present in the bone marrow in large numbers.
- *Subleukaemic leukaemia*: neoplastic cells are present in low numbers in peripheral blood but are present in the bone marrow in large numbers.
- *Myelodysplasia*: peripheral cytopenia with hypercellular marrow; the marrow shows abnormal maturation, but <30% blast cells (preleukaemia).
- *Myelophthisis*: occupation of the bone marrow by neoplastic cells, 'crowding out' the normal bone marrow.
- *Myelofibrosis*: proliferation of fibrous elements in the marrow space; haematopoiesis is not sustainable.

Lymphoid leukaemias

The lymphoid leukaemias are the most common leukaemias seen in the dog, with chronic lymphocytic leukaemia (CLL) the most frequently diagnosed and treated. Myeloid leukaemias are extremely rare. When diagnosing a leukaemia it is important to differentiate lymphoid from myeloid leukaemia and lymphoid leukaemia from stage V lymphoma (Table 22.4). The aetiology of leukaemia in the dog is currently unknown; no retrovirus has been discovered and documented genomic alterations are currently not identified.

The clinical signs of any leukaemia can be varied, with severity of signs greater in patients with acute leukaemia. Common signs include lethargy, anorexia, weight loss, anaemia, bleeding diathesis and PU/PD.

Clinical evaluation

- Physical examination: assess lymph nodes and spleen.
- Splenomegaly: due to infiltrative disease.
- Peripheral lymph node enlargement: lymphoma should be ruled out.
- Pallor: evidence of anaemia (the anaemia is generally non-regenerative).
- Bleeding: can be due to thrombocytopenia, coagulopathy or hyperviscosity.
- Fever: secondary to infection or paraneoplastic cytokine production; more common with lymphoid leukaemias.
- Neurological signs: neoplastic infiltrates around the meninges, haemorrhage or hyperviscosity.

Table 22.4 Comparison of stage V lymphoma (LSA) and chronic lymphocytic leukaemia (CLL)

Physical findings	Stage V LSA	CLL
Clinical signs	Moderate duration with progression	Asymptomatic to slowly progressive
Lymph nodes	Moderate to massive enlargement	Mild enlargement
Spleen	Mild to moderate	Mild to moderate
Anaemia	Mild to moderate	Mild to moderate
Total white blood cell count	Normal to increased	Usually increased
Lymphocyte count	Normal to increased	Increased
Lymphocyte morphology	Normal to moderate atypia	Normal to mild atypia
Bone marrow	Mild to moderate infiltration with atypical lymphoid cells	Marked infiltrate with normal to mildly atypical lymphoid cells
Other organs	Often involved	Rarely involved
Paraneoplastic syndromes	May be seen	Rarely occur

Diagnostic work-up

- Haematology with smear evaluation, biochemistry and urinalysis, coagulation profile.
- Radiographs: chest and abdomen.
- Abdominal ultrasound.
- Flow cytometry.
- Bone marrow aspirate/biopsy: a good quality aspirate is sufficient in patients with a high white count but in patients with a low count a core biopsy is indicated. Good locations for bone marrow biopsy are the humerus and iliac crest.

Prognosis

Prognosis is dependent on the type of leukaemia.

Chronic lymphocytic leukaemia (CLL)

Older dogs (median age 10.5 years) are affected more than younger dogs; there is no known gender or breed predisposition. The disease can have a protracted course over a number of years. Patients are often asymptomatic, with the condition

being detected on routine blood work for another problem. A mild anaemia is common.

Physical examination findings may reveal mild to moderate splenomegaly or possibly mild lymphadenopathy.

Diagnosis is based on elevated white blood cell count with a lymphocytosis; a bone marrow aspirate will confirm the diagnosis. In dogs, ~70% of CLL are of T-cell origin (CD3+), with a large proportion of these cells having large, granular lymphocyte morphology (LGL).

Prognosis

The prognosis is good with survival times up to 2–3 years.

Treatment

Treatment is recommended for dogs with white counts in excess of 50 000. Once the white count has normalized and stabilized, treatment can be discontinued.

- Chlorambucil 0.2 mg/kg once daily for 10 days, then 0.1 mg/kg once daily until the white count is normal.
- Prednisolone at 30 mg/m^2 once daily tapered slowly over a 3-week period.
- In cases where either the initial count is very high or response is slow, vincristine 0.7 mg/m^2 can be given.

Acute lymphoblastic leukaemia (ALL)

No age or sex predisposition is known. ALL is seen most frequently in large breed dogs (e.g. German Shepherds, Rottweilers).

The clinical signs can be acute with a median duration of 2 weeks prior to diagnosis. Typical presenting signs include lethargy, anorexia, PU/PD and shifting leg lameness.

The diagnosis is made based on large numbers of circulating blast cells in the blood and bone marrow; anaemia and thrombocytopenia are common haematological abnormalities. Flow cytometry is advised to confirm the lymphoid origin of the blasts. Dogs with ALL often have significant splenomegaly and minimal lymphadenopathy.

Prognosis

Prognosis is guarded. However, with the advent of flow cytometry we are more confident in treating patients with ALL and improved chemotherapy protocols may also increase long-term survival in these patients. Prompt treatment is required with the necessary supportive care. The higher the white cell count, the greater the risk of tumour lysis syndrome (TLS) (see Chapter 10), and intravenous fluid support is needed.

For severely anaemic or thrombocytopenic patients, access to blood products is essential. These patients are also often neutropenic (or potentially so), and broad-spectrum antibiotics are required as infection can be a serious problem. Colony-stimulating factors may be beneficial.

Treatment

The ideal protocol would reduce cell number quickly without toxicity. It does not exist. The higher the cell count, the greater the risk of TLS, and concurrent neutropenia and thrombocytopenia mean that dogs are either given a standard COP or CHOP protocol or a 'diluted' version of an existing protocol (Matus 1989) in an attempt to prevent side effects. This means that drug resistance will develop early, with the result that less than 10% of patients achieve a 1-year survival (Matus 1989). It is these patients that would benefit the most from more aggressive therapy (BMT, radiation) if we are to increase survival times. Patients with ALL are best treated at a specialist centre where adequate supportive care is available.

Non-lymphoid leukaemias

The myeloid leukaemias are uncommon in dogs.

Chronic myeloid leukaemia (CML)

CML is extremely rare with no breed or gender predisposition. Median age is 6–7 years. Lethargy and fever are common presenting clinical signs, other signs are non-specific. On clinical examination hepatosplenomegaly is common.

In itself the diagnosis of CML is often a diagnosis of exclusion as it is sometimes difficult to differentiate between CML and a leukemoid response. White blood cell counts can range from 16000 to 170 000.

Treatment

The drug of choice is hydroxyurea (50 mg/kg sid or divided bid, then every other day when blood count is normal) (Leifer et al 1983). A second line drug is busulfan (0.1–0.2 mg/kg daily until nucleated count has normalized) (MacEwen et al 1975). Prognosis is fair with an MST of 1 year; patients may eventually develop a blast crisis. Imatinib mesylate (Gleevec) is currently an important drug in the management of human patients with Philadelphia-positive CML (Cohen et al 2002).

Acute myelogenous leukaemia (AML)

AML is a rare cancer with no known breed or sex predilection, but is more common in large breed dogs. Age range is from 1 to 12 years with a median of 6 years. The clinical signs can be similar to ALL, but ocular signs are more common with AML.

The diagnostic work-up is the same but it is essential that AML be distinguished from ALL via immunocytochemistry. ALL and AML can be difficult to distinguish morphologically. The white blood cell count can be extremely variable, with a range from 1500 to 300 000.

Treatment

The prognosis for AML is extremely guarded with a generally poor response rate. It is hoped that with better and earlier diagnosis, treatment options will improve for these patients with better survival times. Currently, combination chemotherapy is recommended based on cytosine arabinoside, doxorubicin and 6-thioguanine. There is no standard protocol. Patients with AML should be treated at a specialist facility.

Other myeloproliferative disorders (MPDs)

These are rare in the dog and include:

- *Acute*: erythroleukaemia, megakaryoblastic leukaemia, monocytic leukaemia, myelomonocytic leukaemia, myeloblastic leukaemia and acute undifferentiated leukaemia. They all carry a poor prognosis and often immunocytochemistry is needed to differentiate them.

Overall clinical signs result from accumulating blast cells in the bone marrow and sometimes the bloodstream, resulting in progressive cytopenias. Even with aggressive chemotherapy, responses – when they occur – are not durable.

- *Chronic*: polycythaemia vera (primary erythrocytosis), basophilic and eosinophilic leukaemia, essential thrombocythaemia. These conditions have a more insidious clinical course and patients may live for months or years. In some cases a 'blast crisis' may occur, leading to rapidly progressive disease. Hydroxyurea is the drug of choice.

For a full discussion of these conditions, see Young & MacEwen (2001).

FELINE LYMPHOMA

Like its canine counterpart, feline lymphoma is one of the most commonly diagnosed malignancies in the cat and accounts for approximately 33% of all feline malignancies. It is here that the similarity ceases. Canine lymphoma is predominantly multicentric, with nasal and intestinal forms being seen much less frequently, whereas in cats intestinal disease is the most common location and isolated forms such as nasal lymphoma are seen much more frequently and multicentric disease is seen far less frequently. Mediastinal lymphoma is seen in both species (Table 22.5).

Role of feline leukaemia virus (FeLV)

The incidence of FeLV-positive lymphoma continues to decline due to continued vaccination. However, for those cats that are FeLV positive the prognosis remains poor compared to negative patients. Typically feline lymphoma has been seen in young FeLV-positive cats with mediastinal disease or older FeLV-negative patients with gastrointestinal disease. In the absence of the virus, the median age for developing lymphoma is 10 years. Breed predisposition is seen in mediastinal lymphoma where young Siamese cats are over-represented (Louwerens et al 2005). The presence of feline immunodeficiency virus (FIV) may contribute to the development of lymphoma (Terry et al 1995).

Histological classification

Histological classification of feline lymphomas is based on defining sub-types of disease in relationship to the expected biological behaviour of the tumour in the patient. Feline lymphomas are therefore considered to be of low–intermediate or high grade (Valli et al 2000). Using this system, 54% and 35% are of high or intermediate grade, respectively, and would be expected to behave accordingly.

Approximately 75% of feline lymphomas are of B-cell origin, whilst mediastinal and leukaemic forms are generally T-cell (Gabor et al 1999). Alimentary forms have been described by different groups as being either of B- or T-cell origin; feline intestinal lymphoma may require more specific tools such as molecular clonality to fully determine the dominant genotype (Moore et al 2005, Werner et al 2005).

Clinical signs

These are dependent on location. Typically, for intestinal forms of the disease, non-specific gastrointestinal signs are common, e.g. weight loss, anorexia, vomiting, diarrhoea or in

Table 22.5 Anatomical location of feline lymphoma and response to therapy

Anatomical location	Frequency	FeLV status	Prognosis with treatment	Comments
Gastrointestinal tract	Most common presentation, 30–50% of cases	Majority are negative	Median 10–12 months based on doxorubicin-based protocols	Can be isolated or diffuse
Multicentric	20–30% of cases	Approximately one-third are positive	Poor survival times for FeLV-positive cats	–
Mediastinal	10–20% of cases	Young: high frequency of positive cats Older: low frequency of positive cats	Poor survival times for FeLV-positive cats 2–3 months; older cats that are FeLV negative have a fair prognosis	Mediastinal lymphoma in older cats is relatively rare, but can respond well to chemotherapy or radiation Main differential is thymoma
Renal	5% of cases	Approximately one-quarter are positive	FeLV-positive cats: median survival 3–6 months; FeLV-negative cats can have long survival times depending on renal function	CNS involvement common, therefore cytarabine arabinoside should be included in any protocol
Nasal	5% of cases	Majority are negative	Good prognosis with radiation	Important to diagnose and treat early
Spinal/CNS	<5% of cases	–	Poor prognosis	Radiotherapy should be considered for isolated spinal disease
Single node	Unknown, but rare	Unknown	Believed to be good as this may represent indolent disease	

some instances weight loss with a good appetite. In the latter cases hyperthyroidism would be the primary differential.

Clinical evaluation

Good physical examination is important and with gastrointestinal lymphoma a mass may be palpable on examination, or the intestines may feel thick and 'ropey'. Nasal lymphoma may present as either a unilateral or bilateral nasal discharge with varying degrees of upper respiratory distress. Patients with mediastinal lymphoma usually present with acute respiratory distress and on radiographs a large mass is present in the anterior mediastinum. Patients with multicentric disease usually present because the client has noticed a lump.

Diagnostic work-up

The relevant diagnostics depend on the clinical history of the patient. However, a minimum database should be established for every patient to include biochemistry, haematology, FeLV, FIV, T4 (if appropriate), and urinalysis.

Prognosis

Unlike dogs, few useful prognostic indicators have been established and those that have primarily centre on the extent of disease. Patients with more advanced disease, and those with multi-organ involvement or that are clinically ill (substage b), have been shown to have a poorer prognosis (Mooney et al 1989, Vail et al 1998), emphasizing the importance of early diagnosis and treatment. Other negative prognostic factors include failure to achieve a complete remission (Teske et al 2002, Vail et al 1998) and positive FeLV status (Mooney et al 1989).

Staging

Staging, as carried out for canine lymphoma, has not been shown to be consistently prognostic in feline disease (Milner et al 2005) and anatomical location was also not shown to be prognostic in one study (Gabor et al 1998). However, with isolated forms of the disease, especially nasal lymphoma, the prognosis is generally good (with early diagnosis and appropriate treatment) (see Chapters 7 and 14).

Treatment

Chemotherapy

Chemotherapy is the major treatment modality in the management of feline lymphoma and, as in the dog, a number of treatment protocols are to be found in the veterinary literature. The most frequently used protocols are CHOP or COP based, with or without L-asparaginase (Cotter 1983, Hadden et al 2008, Kristal et al 2001, Moore et al 1996, Teske et al 2002, Zwahlen et al 1998).

There is some controversy as to the overall benefits of including doxorubicin in protocols for feline lymphoma; however a number of large studies have shown a survival benefit of including doxorubicin in the protocol (Moore et al 1996, Vail et al 1998), whereas only one European study showed equally good response rates with COP alone (Teske et al 2002). This may reflect the different populations considered in the studies, especially as in the European study only seven cats (11.5%) had alimentary disease.

The authors advise the incorporation of doxorubicin in the management of patients with intermediate or high-grade lymphomas, but in the small percentage of patients with low-grade lymphocytic lymphomas the authors would not treat these patients as aggressively. Slowly progressive low-grade disease does not necessarily need to be treated aggressively and therefore protocols that we associate with more benign conditions (e.g. CLL) such as prednisolone and chlorambucil may be more appropriate (Fondacaro et al 1999). In one study (Kiselow et al 2008), cats with lymphocytic lymphoma were treated with chlorambucil (20 mg/m^2 orally every 2 weeks) and prednisolone (5 mg once daily for 14 days and then every other day); 56% of cats achieved a complete response (median remission duration 897 days), 39% achieved a partial response (median remission duration 428 days) and only 5% did not respond.

In addition to low-grade lymphocytic lymphoma there is a distinct variant of intestinal lymphoma, known as large granular lymphoma (LGL) (Darbes et al 1998, Franks et al 1986). This was also known as 'large granular lymphocyte lymphoma' or 'tumours of globular leucocytes'. The neoplastic cells are natural killer (NK) cells and cytotoxic T-cells (CD3, CD57, perforin+, CD20–). They typically arise in the small intestine (jejunum or mesenteric lymph nodes). LGL is an aggressive neoplasm and it rapidly metastasizes to various organs, including lung, myocardium, salivary gland and spinal cord, and is poorly responsive to chemotherapy, although a few long-term responses have been reported.

Unfortunately, whatever protocol is selected, the majority of cats will relapse and the same issues result as to selection of salvage protocols as with canine patients (see canine section).

Hodgkin's-like lymphoma

This is a distinct form of nodal lymphoma in cats that involves single or regional lymph nodes of the head and neck (Day et al 1999, Walton & Hendrick 2001). Its histological appearance is similar to human Hodgkin's lymphoma, hence the name.

Currently the treatment of choice is excision of the affected lymph node, followed by close monitoring. At present there appears to be no indication for chemotherapy in these patients.

Anecdotally, the author (SN) treated one patient with radiation (8 Gy/treatment for three treatments). The decision to treat with radiation was made because of the isolated nature of the disease and the fact that this node had been previously incompletely removed and was at the time of treatment deeply attached and no longer easy to remove surgically. A complete response occurred with no recurrence over a 9-month period (time of writing).

Cutaneous lymphoma

Providing the lymphomatous mass is solitary, surgical excision is the treatment of choice. For isolated masses not ame-

nable to surgery, radiotherapy is the treatment of choice. Very little is published on chemotherapeutic protocols in the management of cutaneous lymphoma in cats, but there is no reason to believe that it would be more chemotherapy responsive than in dogs. In patients with multiple lesions it would seem rational to consider CCNU as an appropriate agent.

Radiotherapy

Radiation has a limited application in the treatment of feline lymphoma. However, it is the treatment of choice for cats with isolated nasal lymphoma. A complete response is seen in the majority of patients (80–100%), with median remission greater than 18 months (Straw et al 1986). A short hypofractionated course of treatment is usually sufficient (8 Gy given in 3-weekly fractions is the authors' preferred protocol). Side effects from treatment include inflammatory rhinitis, which usually resolves within a few weeks of finishing treatment. Survival times for patients with nasal lymphoma treated with chemotherapy are inferior to those treated with radiation (151–380 days). A recent study (Sfiligoi et al 2007) evaluated the benefit of combined radiotherapy and chemotherapy; all cats received megavoltage radiation (median dose 42 Gy) and a 6-month course of chemotherapy. The median survival time was 31.4 months.

Radiation also has a role in the emergency management and continuing management of patients with mediastinal lymphoma and may also be considered for patients with isolated Hodgkin's-like nodal lymphoma. Other indications would include lymphoma of the CNS and spinal cord.

Surgery

Obtaining surgical biopsies remains the most accurate means of diagnosing intestinal lymphoma, and surgical excision of solitary intestinal lymphomas is recommended in conjunction with chemotherapy (see Chapter 15). Surgical excision of solitary cutaneous masses is the treatment of choice, but primarily surgery is required for diagnostic purposes rather than curative intent.

Lymphoid leukaemias

In cats, ALL is linked with FeLV status as greater than two-thirds of cats with ALL are FeLV positive; most cats with CLL are FeLV negative. For FeLV-positive cats with ALL the prognosis is poor, because even with aggressive chemotherapy responses are of short duration with less than 10% of cats surviving 6 months. CLL is extremely rare in the cat and long-term survival figures are essentially unknown.

Non-lymphoid leukaemias

These are rare in the cat and, as with the dog, immunocytochemical stains are usually required to determine lineage. The prognosis for patients with acute disease is poor; chronic leukaemias have a better prognosis.

Plasma cell tumours

Plasma cell tumours result from transformation of cells of B-lymphocyte lineage and as such may be secretory.

Solitary plasmacytoma

These tumours can originate in either bone or soft tissues and are characterized by their site of origin, extramedullary plasmacytoma (EMP) and solitary osseous plasmacytoma (SOP); the latter may eventually progress to multiple myeloma.

Generally, these are considered to be relatively benign tumours when they arise in the mouth or skin; however, intestinal tumours are more aggressive with early metastasis to regional lymph nodes.

Clinical signs

Solitary plasmacytomas are rarely secretory so clinical signs depend on location. Those of the cutaneous tissues and oral cavity usually present because the client has noticed a lump. SOP is usually associated with pain, and radiographs reveal a lytic lesion in the affected bone; patients with vertebral plasmacytomas may present with neurological signs. Intestinal plasmacytomas will elicit typical intestinal signs of vomiting and anorexia.

Diagnostic work-up

A tissue biopsy is required. For poorly differentiated tumours immunohistochemistry may also be necessary. As it is important to confirm the solitary nature of a plasmacytoma before starting treatment, skeletal radiographs, serum electrophoresis and bone marrow aspirates are required.

Treatment

For solitary plasmacytomas the treatment of choice is either surgical excision with adequate margins or external beam radiation. Treatment selected depends on location and potentially the size of the surgery, e.g. with oral plasmacytomas. For very large oral tumours the surgical dose can be reduced by treating with radiation first, shrinking the tumour to allow a smaller, more cosmetic surgery to follow. Prognosis with complete local control is good (Wright et al 2008). For patients with SOP of the appendicular skeleton, systemic chemotherapy should be considered.

The likelihood that SOP may progress to multiple myeloma means that these patients should be monitored regularly after local control has been established. This would entail routine checkups and monitoring of plasma proteins for evidence of systemic spread.

Multiple myeloma and Waldenstrom's macroglobulinaemia

Multiple myeloma accounts for approximately 8% of canine malignancies and is seen less frequently in cats. In dogs, approximately 33% are hypercalcaemic.

Clinical signs

The majority of patients with myeloma present with signs associated with hypercalcaemia (PU/PD, anorexia, vomiting),

hyperviscosity (PU/PD, lethargy, epistaxis, retinal haemorrhage, seizures), renal failure (PU/PD, vomiting, lethargy), bone pain or pathological fracture. In some instances elevated proteins/globulins are found on routine blood work, prompting a further work-up.

Diagnostic work-up

For the patient with suspected multiple myeloma, diagnosis is based on the following criteria (usually two out of four are sufficient for a diagnosis):

- osteolytic bone lesions
- serum myeloma proteins (M-component)
- bone marrow plasmacytosis
- Bence-Jones proteins in the urine.

For all patients a minimum database should be established to include haematology (anaemia may sometimes be significant), biochemistry (renal parameters and ionized calcium in particular) and urinalysis (proteinuria, urine protein/creatinine to rule out paraneoplastic glomerulonephropathy). Serum electrophoresis is required to confirm the presence of a monoclonal gammopathy and characterize the immunoglobulin component. In dogs this is equally divided between IgG and IgA; if the M-component is IgM the term Waldenstrom's macroglobulinaemia is applied. In cats the immunoglobulin is usually IgG.

For analysis of Bence-Jones proteins a urine sample must be submitted to an outside laboratory for analysis. These are immunoglobulin light chains and are not detected on urine dipsticks.

Abdominal ultrasound is recommended as part of staging as liver, spleen and lymph nodes can be involved, especially with macroglobulinaemia. If these organs appear abnormal, FNA should be taken.

Hyperviscosity can result in ocular disease so a fundic examination is important. Retinal haemorrhage, venous dilation and tortuous vessels may be seen; in severe cases retinal detachment and blindness may occur.

It is important to assess skeletal lesions but biopsy is rarely indicated in the presence of other positive tests.

Other conditions that result in a monoclonal gammopathy include:

- secretory B-cell lymphomas/leukaemias
- chronic infections – ehrlichiosis, feline infectious peritonitis (FIP), leishmaniasis (although these are often polyclonal rather than monoclonal).

Monoclonal gammopathy of unknown significance is also reported.

Treatment and prognosis

The treatment of choice for multiple myeloma is melphalan and prednisolone chemotherapy. There are a number of slightly different dosing regimens but the authors generally start canine patients on 0.1 mg/kg melphalan for 10 days and then reduce the dose to 0.05 mg/kg once daily until remission is achieved (Hohenhaus 1995). Prednisolone is started at 1 mg/kg daily and tapered off over a 4-week period.

Initially haematology and total globulins are checked every 2 weeks to monitor response and then monthly thereafter. In patients that achieve a complete response and proteins remain stable for 3 months, treatment can be discontinued but it is important to monitor these patients closely for relapse. The availability of oral bisphosphonates, e.g. alendronate, means that these drugs can be used in addition to chemotherapy and hopefully will reduce the risks of pathological fractures. For patients with a large tumour burden a more aggressive induction can be given, either another alkylating agent such as cyclophosphamide, or vincristine.

Providing the patient has not presented in renal failure, the overall prognosis for multiple myeloma is good, with survival times in excess of 18 months. When relapse occurs the authors find that changing the alkylating agent (chlorambucil or cyclophosphamide) will often give a second remission. Many patients will eventually succumb to renal failure resulting from the glomerulonephropathy associated with paraproteins produced by the plasma cells. In other instances patients will present with pathological fractures from progressive disease.

Feline patients with multiple myeloma have been reported to have a poorer prognosis. A recent multi-institutional study (Mellor et al 2006) evaluated 24 cats with myeloma-related disorders and classified presentation in two groups. In the first group tumour involved the abdominal organs, bone marrow or both. A small number of cats in this group (7) received chemotherapy with a median survival time of 12.3 months. The second group had cutaneous involvement and for those cats without systemic signs, excision of the skin masses gave long-term survival (greater than 2 years). Earlier studies were not as encouraging, with only transient response to melphalan and prednisolone and a median survival time in the order of 2–3 months (Drazner 1982), although numbers in earlier studies were small.

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Tumours of the spleen

The spleen performs a number of functions in the body, one of which is as a secondary organ of haematopoiesis. This function usually ceases at birth but in dogs a limited capacity remains and is known as extramedullary haematopoiesis. It is seen in adult animals with extra demand, due either to infiltrative disease of the marrow or spleen or excessive destruction of erythrocytes. The spleen has a reservoir capacity and can store between 10 and 20% of the total blood volume of the dog. It is also a major filtration organ and is the principal site of IgM production in both the dog and cat. A number of tumours can arise from the spleen or infiltrate it.

Tumours affecting the spleen can do so by infiltrating the organ throughout, causing generalized splenomegaly or discrete masses. Tumours of myeloproliferative origin, lymphoma (LSA), mast cell tumour (MCT) and histiocytic disorders are the most commonly occurring tumours to cause diffuse enlargement of the spleen. Inflammatory disease, splenitis or extramedullary haematopoiesis in the dog are the most common non-neoplastic conditions that cause diffuse splenomegaly. In cats the most common splenic tumours are LSA and MCT.

Tumours that arise from the mesenchymal elements of the spleen typically give rise to isolated splenic masses; however, some tumours such as MCT or LSA can do both. Non-neoplastic splenic masses are more common than neoplastic ones but it can be difficult to distinguish between them without surgery. The most common malignant tumour of the spleen in dogs is haemangiosarcoma (HSA); other malignant tumours include leiomyosarcoma, fibrosarcoma (FSA), histiocytic sarcoma (HS), liposarcoma and osteosarcoma (OSA); benign tumours include haemangioma, fibroma, leiomyoma and myolipoma; other splenic disease that may appear neoplastic includes nodular hyperplasia, haematoma and abscess. Fibrohistiocytic nodules comprise both the benign elements of nodular hyperplasia and the more malignant characteristics of a sarcoma (Spangler & Kass 1998).

Clinical signs of splenic neoplasia

Patients with splenic disease can present with a number of clinical signs depending on the underlying cause. These can include anorexia, vomiting, polyuria/polydipsia (PU/PD), acute abdominal pain, weakness, pale mucous membranes, collapse or in some cases the client has noticed abdominal swelling.

Diagnostic work-up

Presenting clinical signs, followed by a thorough physical examination, will guide the rest of the diagnostic evaluation. Careful abdominal palpation will often reveal the presence of an enlarged spleen, mid-abdominal mass effect or ascites. Abdominal radiographs can be helpful in the absence of any fluid. Routine haematology may show anaemia sufficient to indicate haemorrhage or elevated white blood cell count, which may be either a mature neutrophilia (seen in patients with HSA or splenic torsion) or abnormal lymphoid/myeloid cells (leukaemia). Coagulation profiles and platelet counts should be checked because of the high incidence of disseminated intravascular coagulation (DIC) in patients with splenic disease.

Abdominal ultrasound provides valuable information as to the size, location and echogenicity of masses within the spleen. It also provides information in the case of generalized splenomegaly because infiltrative disease will often give a 'Swiss cheese' effect to the parenchyma. Fine needle aspirates (FNA) or tru-cut biopsies of the spleen can be taken and are particularly helpful in diagnosing LSA, leukaemia and MCT (**Figure 23.1A**) and in ruling out non-neoplastic conditions such as splenitis (**Figure 23.1B**).

The risk/benefit of biopsying a splenic mass is debatable and depends on the overall appearance of the spleen: a large solitary bleeding mass requires surgery; multiple nodules (nodular hyperplasia or fibrohistiocytic nodules) may be biopsied by ultrasound guidance; diffuse infiltrative disease can be diagnosed on FNA. The entire abdominal cavity should be examined with ultrasound prior to surgery, if possible. In some cases the tumour can be so large that other organs cannot be visualized easily, or the amount of fluid makes complete examination difficult. However, ultrasound findings should not be over-interpreted, e.g. nodular changes in the liver cannot be definitively diagnosed as metastasis on the basis of image alone.

Thoracic radiographs should be taken before any surgery.

Treatment

The treatment of choice for splenic masses is splenectomy. It is important to remember that up to 50% of splenic masses are benign or low grade and have a good prognosis with successful surgery.

Biopsies should be taken of liver (even if grossly normal) and any other abdominal pathology, if feasible. More than one dog has had ectopic splenic nodules, not metastatic HSA. Bleeding liver mass(es) may also be removed if possible, to control haemorrhage.

Animals with splenic masses may experience complications of surgery and anaesthesia because of anaemia, thrombocytopenia, hypoproteinaemia, DIC, hypovolaemia, hypotension, hypoxaemia, cardiac arrhythmias and uncontrollable haemorrhage. In cases with considerable, rapid blood loss into the abdominal cavity, a pressure bandage applied to the abdomen

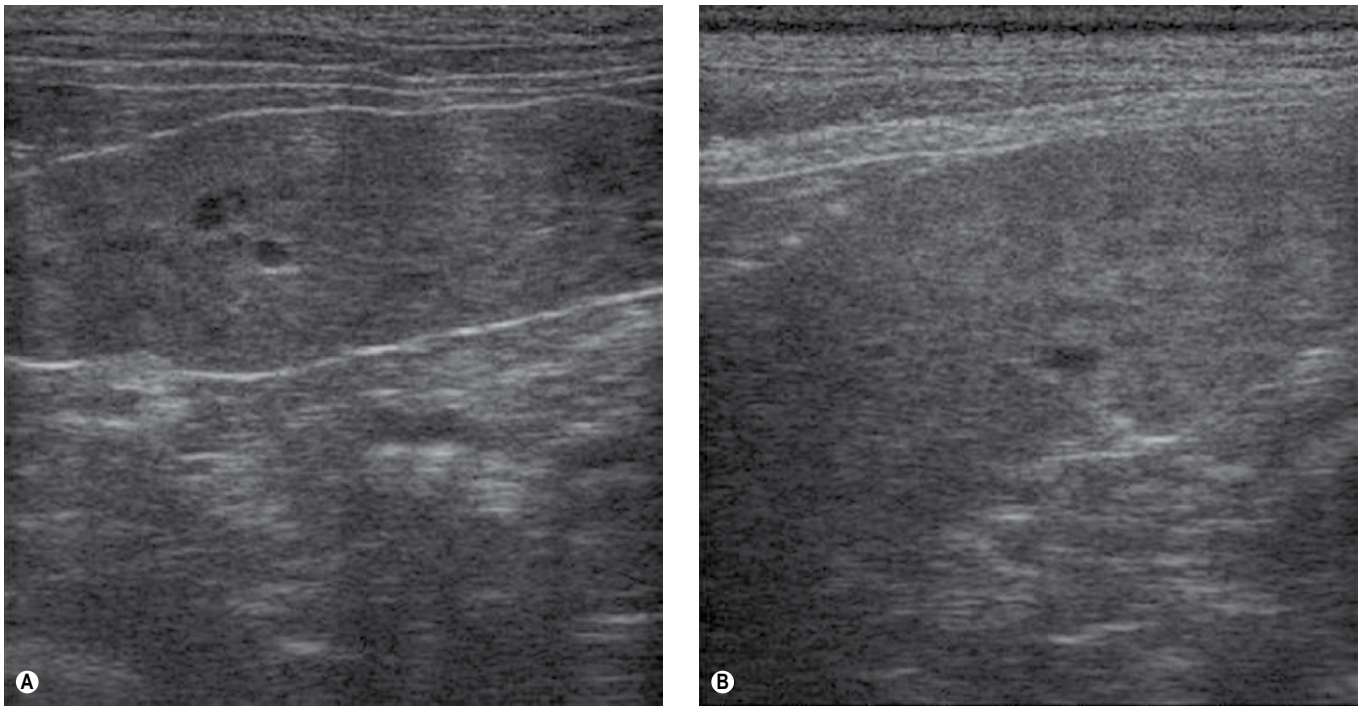


Figure 23.1 Ultrasound scan of (**A**) splenic lymphoma, (**B**) splenitis.

may help stem bleeding while the patient is made stable enough for surgery via intravascular fluid volume replacement, oxygen support, blood products, colloids and the like. Use pressor support with dopamine, dobutamine is also useful; atropine and adrenaline are also kept on hand.

The surgery to stop the bleeding (i.e. splenectomy) should not be delayed unnecessarily, but also not performed if the patient is thought to benefit from further short-term stabilization. In the postoperative period, blood products may still be needed (Chapter 9), but for any patient in DIC removal of the tumour should result in rapid normalization of clotting times. A continuous ECG is required to monitor for cardiac arrhythmias; this is a common occurrence post splenectomy and may not occur until 48 hours after surgery. Intervention to correct the arrhythmia is dependent on its severity and if the patient is showing clinical signs. Lidocaine infusions should be used if required and then switched to oral mexiletine for a few days.

CANINE TUMOURS

Splenic haemangiosarcoma (HSA)

Splenic HSA is the most common canine neoplasm of the spleen and the most common presentation of HSA in the dog. In one study of 500 cases of splenomegaly, the ratio of benign to malignant disease was about 50:50, and HSA made up 51% of splenic malignancies (Spangler & Kass 1997). Another study showed that of 100 cases of splenomegaly in dogs, two-thirds had malignant disease, and two-thirds of those malignancies were HSA (Johnson et al 1989). In another study of 87 cases of splenic abnormality, about 50% were neoplastic, and 44% of these were HSA (Day et al 1995). It is typically seen in older dogs with a median age of 9 years, although young dogs may be affected. Breed predispositions include German Shepherds, Golden Retrievers and Labrador Retrievers (Brown et al 1985, Day et al 1995) (**Figure 23.2**).

In another study of over 1500 cases, splenic haematoma and hyperplastic nodules made up the bulk of splenic lesions, but HSA was the most frequent neoplasm. Splenic haematoma and HSA were grossly indistinguishable in most cases (Spangler & Culbertson 1992).

HSA is highly metastatic and spreads haematogenously. The primary metastatic site is the liver, but up to 25% of dogs with splenic HSA have tumour in the right atrium (Waters et al 1988). Direct seeding of tumour through the omentum and mesentery can occur when these tumours bleed or rupture. Other metastatic sites include the lung, skin and brain.

Clinical signs

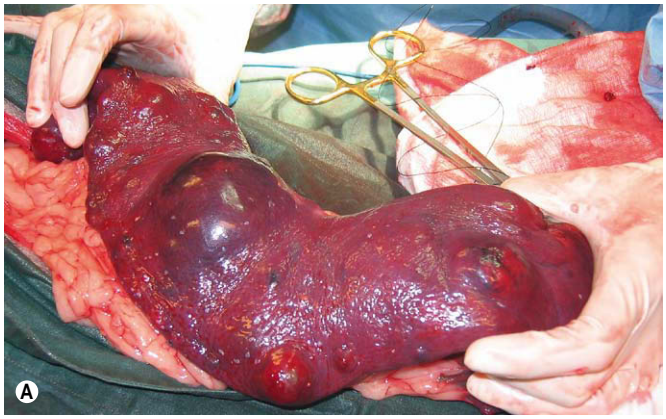
Clinical signs are typically associated with blood loss, either generalized weakness or acute collapse; however, some patients will present for lethargy without obvious signs of haemorrhage. If the bleed has been severe due to splenic rupture, the patient may present with very pale mucous membranes and in haemorrhagic shock. A packed cell volume (PCV) will quickly show the degree of anaemia.

Diagnostic work up

- *Haematology*: leucocytosis is common with HSA, anaemia can be due either to acute blood loss or secondary to destruction of red cells passing through the abnormal blood vessels of the tumour (microangiopathic).
- *Abdominal radiographs*: the mass can be small or obscured by fluid.
- *Abdominal ultrasound*: a complex hypoechoic mass is characteristic of HSA and the presence of blood-filled

cavernous spaces means presurgical biopsy is unlikely to be rewarding and may cause significant haemorrhage. It is important to evaluate the liver to rule out potential metastases. The major differentials that will appear to be very similar to HSA on ultrasound are haemangioma and haematoma, and in all instances the treatment of choice is splenectomy.

- *Abdominocentesis*: this is indicated in the presence of an effusion, and if it is 'bloody' in appearance, then the PCV should be taken and compared with the peripheral blood PCV (**Figure 23.3**).



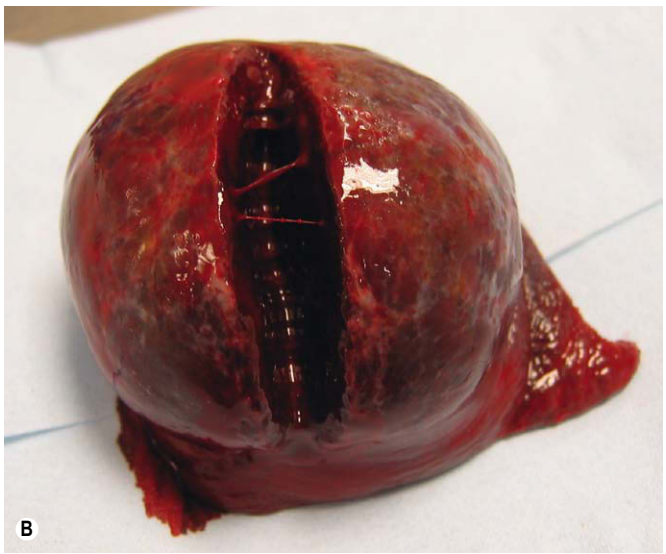


Figure 23.2 (**A, B**) Splenic haemangiosarcoma.

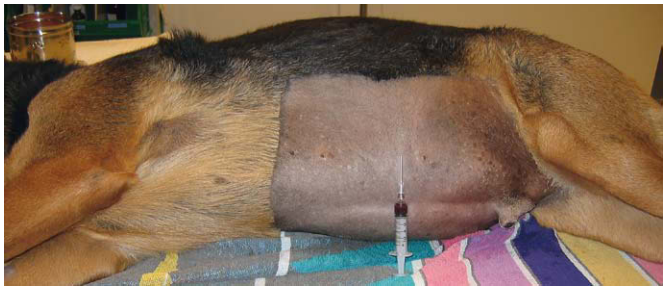


Figure 23.3 Abdominocentesis on a dog with haemoabdomen.

- *Thoracic radiographs/CT*: required to rule out metastatic disease that could make surgery contraindicated.
- *Coagulation profile*: this should be obtained prior to surgery; however, if this is not possible then an activated clotting time and buccal mucosal bleeding time are helpful.

Staging

Staging is important (see Table 23.1).

Prognosis

The prognosis for dogs with splenic HSA is guarded due to the rapid development of metastasis, primarily in the liver but any organ system can be affected. The median survival time (MST) for dogs with splenic HSA treated with surgery alone is 2 months (range 1–3 months) (there are numerous references for the interested reader, e.g. Kim et al 2007, Prymak et al 1988, Wood et al 1998). The prognosis for patients with haemangioma or haematoma is excellent (Prymak et al 1988).

Some studies have found that stage of disease is prognostic (for stage I disease MST is 345 days, compared to 93 days for stage II and 68 days for stage III when treated with splenectomy and epirubicin) (Kim et al 2007). Vail et al (1995) and Sorenmo et al (2000) also found longer survival in stage I versus stage II disease when treated with adjuvant chemotherapy. Others have found no difference in survival with clinical stage (Wood et al 1998) when treated with splenectomy alone or with splenectomy and adjuvant chemotherapy and/or immunotherapy (Brown et al 1985).

Chemotherapy

For dogs with no macroscopic metastases at the time of splenectomy adjuvant chemotherapy has been recommended (Table 23.2). For dogs with evidence of metastasis at the time of surgery the prognosis, even with chemotherapy, is poor.

Chemotherapy protocols include:

- single-agent doxorubicin
- doxorubicin/cyclophosphamide
- VAC (vincristine, adriamycin (doxorubicin) and cyclophosphamide)
- single-agent epirubicin
- ifosfamide.

It can be seen from Table 23.2 that survival times for all five protocols are similar and because of the severe toxicity that can be encountered with the combination protocols, single-agent doxorubicin is considered the treatment of choice. Additional therapies combining L-MTP-PE with doxorubicin were encouraging but unfortunately as L-MTP-PE is not commercially available, splenic HSA remains a frustrating cancer to deal with as we are still encountering the treatment 'wall'.

Table 23.1 Staging of canine splenic haemangiosarcoma

Stage	Extent of disease
I	Confined to spleen
II	Ruptured spleen, no evidence of metastases
III	Ruptured spleen and metastases

Table 23.2 Chemotherapy protocols used in the management of canine haemangiosarcoma

Protocol	Schedule	Dose	Degree of myelosuppression	Median survival time (days): splenectomy + chemotherapy
Doxorubicin ($n = 46$)	5 cycles at intervals of 3 weeks	Dose 30 mg/m^2 for dogs >10 kg or 1 mg/kg for dogs <10 kg	Monitor for myelosuppression	172 (Ogilvie et al 1996)
Doxorubicin/cyclophosphamide ($n = 22$)	Day 1 doxorubicin and cyclophosphamide i.v. Day 22 repeat cycle for a total of 4–6 cycles	Dose doxorubicin as for SA, cyclophosphamide 100–150 mg/m^2; can use oral at 50 mg/m^2 on days 3, 4, 5, 6	Very myelosuppressive; monitor closely Antibiotics may be required	141–179 (Sorenmo et al 1993, 2004)
VAC (vincristine, doxorubicin, cyclophosphamide) ($n = 6$)	Day 1 doxorubicin and cyclophosphamide Day 8 vincristine Day 15 vincristine Day 22 repeat cycle for a total of 4–6 cycles	Dose doxorubicin and cyclophosphamide as previously, vincristine at 0.7 mg/m^2	Extremely myelosuppressive; monitor very closely and stop if neutrophil count goes below 3000 Antibiotics are likely to be required with this protocol	145 (Hammer et al 1991)
Epirubicin ($n = 18$)	4–6 cycles at intervals of 3 weeks	30 mg/m^2	7 of 18 dogs treated with epirubicin were hospitalized for signs of adverse gastrointestinal effects	144 (Kim et al 2007)
Ifosfamide ($n = 6$)	Up to 375 mg/m^2 every 21 days	350–375 mg/m^2	Neutropenia 7 days after administration; must use MESNA in conjunction with ifosfamide due to high risk of sterile haemorrhagic cystitis	142 (Rassnick et al 2000)

SA, single agent.

Other splenic neoplasms

Lymphoma (LSA)/lymphoid leukaemia

LSA of the spleen can be either a primary or a secondary site. Generally, LSA of the spleen is treated with chemotherapy (see Chapter 22 for protocols), but in some cases splenectomy can be performed (Brooks et al 1987). For dogs with splenic involvement splenectomy does not increase survival time, but by reducing tumour burden reduces the likelihood of complications during induction. In patients with acute lymphoblastic leukaemia, splenomegaly is a common finding on physical examination.

Benign tumours (e.g. leiomyoma, fibroma, lipoma)

Leiomyomas, fibromas and lipomas of the spleen are slow-growing tumours. Clinical signs include anorexia, weight loss, vomiting and diarrhoea. Physical examination is likely to reveal the presence of a mid-abdominal mass that may be a considerable size (**Figure 23.4**). The prognosis with splenectomy is good (Spangler et al 1994). However, good postoperative care is required for patients where the tumours are extremely large.

Splenic sarcomas (non-lymphomatous, non-angiogenic)

Dogs with FSA, undifferentiated sarcoma, leiomyosarcoma, OSA, myxosarcoma, HS and liposarcoma all show severely truncated survival (median 4 months with 80–100% mortality after 12 months) when treated with splenectomy. Mitotic index appears to be prognostic for splenic sarcomas, those with a mitotic index of <9 having a better prognosis (Spangler et al 1994). The primary metastatic site is the liver.

Another paper described splenic leiomyosarcoma, FSA, undifferentiated sarcoma, liposarcoma, osteosarcoma, chondrosarcoma, myxosarcoma, rhabdomyosarcoma and fibrous histiocytoma which also showed poor prognosis with splenec-

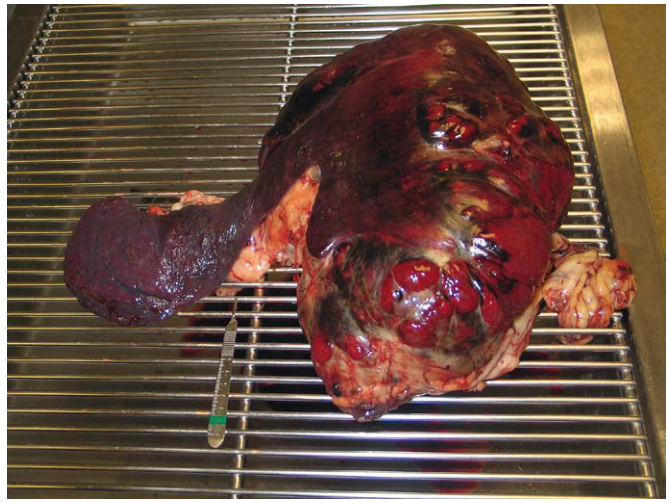


Figure 23.4 Large splenic mass.

tomy (MST 2.5 months overall, MST 9 months if no obvious metastasis at the time of splenectomy) (Weinstein et al 1989).

The role of chemotherapy has not been evaluated, but for patients with undifferentiated sarcomas, or those with high mitotic index, doxorubicin chemotherapy may be of benefit. No published data on the use of chemotherapy in the management of these tumours are available.

Mesenchymomas

These tumours show intermediate survival periods (median 12 months with 50% 1-year survival) (Spangler et al 1994).

Nodular fibrohistiocytic proliferation

According to Spangler & Kass (1998) nodular fibrohistiocytic proliferation is:

> *… characterized by a mixed population of histiocytoid and/or spindle cells in varying proportions intermixed with haematopoietic elements, plasma cells, and/or lymphocytes. These nodules seem to form a continuum between splenic lymphoid nodular hyperplasia and malignant splenic stromal neoplasms (malignant fibrous histiocytoma).*

The 1-year survival is approximately 50%, with an MST of about 5 months (approximately 50% dying of causes related to their splenic disease and 50% dying from unknown or unrelated causes). Post splenectomy mortality was predicted by lymphoid:fibrohistiocytic proportion and mitotic index (better prognosis with a higher proportion of lymphoid to fibrohistiocytic type cells, and lower mitotic index) (Spangler & Kass 1998).

Histiocytic sarcoma (HS) and malignant histiocytosis (MH)

Histiocytic disease affecting the spleen can be classified as systemic histiocytosis (SH), HS (primary or disseminated) or MH (further discussion can be found in Chapter 18).

Origin of histiocytic cells

Histiocytes differentiate from CD34+ precursors into macrophages and dendritic cells (DC), e.g. Langerhans cells. Dendritic cells are antigen-presenting cells with a wide distribution through epithelial sites (cutaneous and mucosal) and these cells constantly migrate through the paracortical areas of lymph nodes.

HS and disseminated HS (formally MH) are seen in a number of breeds including Bernese Mountain Dogs, Flat-Coat Retrievers, Rottweilers, Golden Retrievers and others. HS of the spleen may be found as an isolated lesion, multiple lesions within the spleen or as disseminated disease involving multiple organs (Affolter & Moore 2002).

Splenectomies are recommended when disease appears localized; however, before contemplating surgery, full diagnostic evaluation is required to include abdominal ultrasound, thoracic radiographs/CT, haematology and biochemistry. If evidence of disseminated HS is found the prognosis is poor.

For patients with disseminated disease, partial response to CCNU may occur, and for those with isolated disease that is amenable to surgery CCNU is recommended in the adjuvant setting. In a recent study of 59 dogs diagnosed with HS which had gross measurable (56 dogs) or residual microscopic disease (3 dogs), treatment with CCNU at 60–90 mg/m^2 resulted in an MST of 106 days. An overall response rate of about 50% was achieved for dogs with gross measurable disease, and the three dogs with minimal residual disease experienced tumour relapse but lived 433 days or more after starting CCNU. Thrombocytopenia and hypoalbuminaemia were predictive in that these patients had poorer survival times of <1 month (Skorupski et al 2007).

The authors typically recommend three cycles of CCNU at intervals of 3 weeks (60 mg/m^2) for patients with minimal disease; for those with macroscopic disease, response to treatment is monitored (measuring metastatic foci) and tailoring treatment to suit the individual.

FELINE TUMOURS

The most common feline tumours affecting the spleen are MCT and LSA (Spangler & Culbertson 1992). Diagnosis of either can be made by ultrasound-guided FNA of the liver. For cats with isolated MCT, splenectomy carries a good prognosis with survival times of approximately 12 months, compared to 2 months without surgery (Carpenter et al 1987). Involvement of MCT beyond the spleen to the liver warrants a poor prognosis.

HSA in the cat is rare and accounts for <0.5% of feline tumours. In addition to the spleen, it may arise from liver or mesenteric sites. Intra-abdominal HSA is as aggressive in the cat as the dog, and clinical signs, treatment options and prognosis are essentially identical (Culp et al 2008).

Other tumours of the feline spleen are extremely rare.

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Tumours of the nervous system

TUMOURS OF THE CANINE CNS

Brain tumours occur in dogs more frequently than any other domestic species with a reported incidence of 14.5/100 000 in one US study (Vandevelde 1984). They are typically seen in older dogs (median age 9.5 years). An increased incidence of brain tumours has been reported in Boxers, Boston Terriers, Dobermans and Golden Retrievers (Heidner et al 1991). Brachycephalic breeds, e.g. Boxers, are more likely to develop glial cell tumours whilst dolichocephalic breeds are more likely to develop meningiomas (Summers et al 1995). The aetiology of canine brain tumours is unknown.

Pathogenesis

Brain tumours cause dysfunction either by primary destruction of brain tissue or by compression of adjacent anatomical structures. Increased intracranial pressure is often seen; this is due primarily to oedema and less commonly to haemorrhage or infarction.

As a rule, primary brain tumours grow slowly and therefore have a chronic clinical progression; in many cases this is seen by the client as normal slowing down due to age. Clinical signs are usually only seen when the brain can no longer compensate for the presence of the tumour, and in these cases the onset of neurological signs can be acute and severe. The most common clinical sign seen in patients with intracranial neoplasia is seizures. Therefore, in any older patient presenting with seizures, a primary differential should be a brain tumour. As these tumours are usually advanced at the time of diagnosis, immediate diagnostic evaluation is essential.

Primary brain tumours are usually solitary, but multiple tumours have been reported. The lack of a well-developed lymphatic system within the brain means that major patterns of spread involve local invasion and cerebrospinal fluid (CSF) seeding (LeCouteur & Withrow 2007). Multiple tumours of different histological types may occur rarely. Extracranial metastasis of primary brain meningiomas has been reported, but is considered rare (Schulman et al 1992).

Secondary tumours of the brain are seen due to metastatic spread, e.g. mammary carcinomas, haemangiosarcomas (HSA), prostatic and pulmonary carcinomas (LeCouteur & Withrow 2007). Of these malignancies HSA is seen most frequently and usually when there is evidence of metastasis to brain other extracranial sites are also involved (Snyder et al 2008). CNS lymphoma can occur solely within the CNS or as a secondary tumour late in the course of multicentric lymphoma or simultaneously with the initial presentation of multicentric lymphoma.

Other secondary tumours affect the brain by means of direct local extension, e.g. nasal, frontal sinus, skull, cranial nerve sheath tumours (e.g. oculomotor, vestibulocochlear and trigeminal nerves) or pituitary tumours (see Chapter 26). Skull tumours that affect the brain by local extension include osteosarcoma, chondrosarcoma and multilobular osteochondrosarcoma (LeCouteur & Withrow 2007).

Pathology

Gliomas and meningiomas are the most commonly recognized intracranial neoplasms of dogs, occurring with similar frequencies (Snyder et al 2006).

Glial cell neoplasms are classified based on the predominant cell type (e.g. astrocytoma, oligodendrocytoma). They are often found in the parenchyma of the brain, and can be very invasive.

Meningiomas arise from the arachnoid layer of the meninges; they are peripherally located and most commonly broad based and extra-axial (arise outside of and push into the brain parenchyma) (Bagley 2005a). Canine meningioma is benign, but locally infiltrates along the Virchow–Robin space and invariably lacks demarcation from normal brain tissue. In cats, meningiomas are almost always well defined and have a clear demarcation (LeCouteur & Withrow 2007). The growth rate of meningiomas in cats is slow compared to dogs.

Tumours of the ependyma and choroid plexus include choroid plexus papillomas, which occur relatively infrequently.

CNS lymphoma can be either primary or secondary. Histiocytic lymphoma or neoplastic reticulosis occurs as single or multiple mass lesions characterized histologically by a perivascular proliferation of 'reticulohistiocytic cells' with different patterns of reticulin production, admixed with varying populations of inflammatory cells (LeCouteur & Withrow 2007).

Embryonal tumours of the CNS/primitive neuroectodermal tumours are all derived from a germinal neuroepithelial cell that has the potential to differentiate along a number of neuroectodermal cell lines (neuronal, ependymal, glial). All have an anaplastic nature and are biologically malignant (LeCouteur & Withrow 2007).

Neuronal and mixed neuronal–glial neoplasms (gangliocytoma, ganglioglioma) occur in young animals.

Primary CNS lesions reported rarely include pineal tumours, germ cell tumours (germinoma, teratoma), primary CNS melanoma, chordoma, hamartoma, epidermoid and dermoid cysts and granular cell tumour (LeCouteur & Withrow 2007).

Clinical signs

The most common presenting clinical sign for a patient with a primary brain tumour is seizures (Bagley et al 1999, Snyder et al 2006). Changes in mentation, pacing, circling, head pressing, etc. are also common presenting signs. Other clinical signs can be seen depending on the location of the tumour within the CNS and associated secondary effects of the tumour (oedema, compression of normal brain tissue and increasing intracranial pressure). For example, neoplasms of the cerebellomedullary angle affect the vestibular system, causing vestibular signs, often with brain stem signs (paresis or loss of conscious proprioception), changes in mental status, and deficits in the fifth or seventh cranial nerve. Vertical nystagmus in any head position is most consistent with central vestibular disease. In addition, the nystagmus may change with changing head position (LeCouteur 2003).

Primary brain tumours are typically slow growing. Gradual changes in the individual may have been noticed by the client but attributed to advancing age. This means that the patient has been able to cope for a period of weeks to months before the onset of clinical signs that can be rapidly progressive due to the large size of the majority of tumours at the time of diagnosis. In any patient where a brain tumour is suspected, early diagnostic evaluation is encouraged as early diagnosis will undoubtedly contribute to longer survival times for patients and increase the treatment options available for them. It is essential, therefore, that for any middle-aged to older patient, advanced imaging is recommended. It is to be remembered that the prevalence of epilepsy as a cause of seizures declines rapidly after 5 years of age (Bagley 2005b).

Tumours that grow rapidly or obstruct a major blood vessel may show more acute signs due to haemorrhage or infarction. Metastatic lesions in the brain often lead to acute, rapidly progressive neurological signs. Localized clinical signs are seen most frequently and result from compression, invasion or irritation of a region of the brain, whereas generalized non-localizing signs result from secondary effects, e.g. increasing intracranial pressure (ICP).

Diagnostic work-up

A full neurological examination is required, but in many patients this may be unremarkable. In one study (Snyder et al 2006), 20% of primary intracranial tumours identified were in the olfactory area, an area of the brain that is often associated with a normal neurological examination in spite of the presence of a space-occupying lesion. An ophthalmic examination may be helpful in some patients with increased ICP because papilloedema (optic nerve oedema) may be present. If papilloedema is present, the risk of herniation is increased if CSF collection is planned. It should be remembered that papilloedema could also be seen with inflammatory disease of the CNS.

As with any older patient a minimum database should be established. Haematology, serum biochemistry and urinalysis may assist diagnosis of a primary extracranial malignancy (e.g. pancreatic insulinoma). Thoracic radiographs and abdominal ultrasound are recommended to ensure there is no evidence of extracranial neoplasia or other underlying problems (Snyder et al 2006). Rarely do primary intracranial tumours metastasize, but in patients with multifocal clinical signs, metastatic disease from another tumour should be ruled out.

Imaging, either MRI or CT, is required for definitive diagnosis (**Figure 24.1**). MRI is superior to CT in the evaluation of intracranial neoplasia. In the majority of cases intracranial neoplasms are not amenable to biopsy and the diagnosis is usually presumptive based on the imaging characteristics of the tumour and location within the CNS. CSF analysis is a secondary non-specific test but changes in CSF have been associated with intracranial tumours, the most common

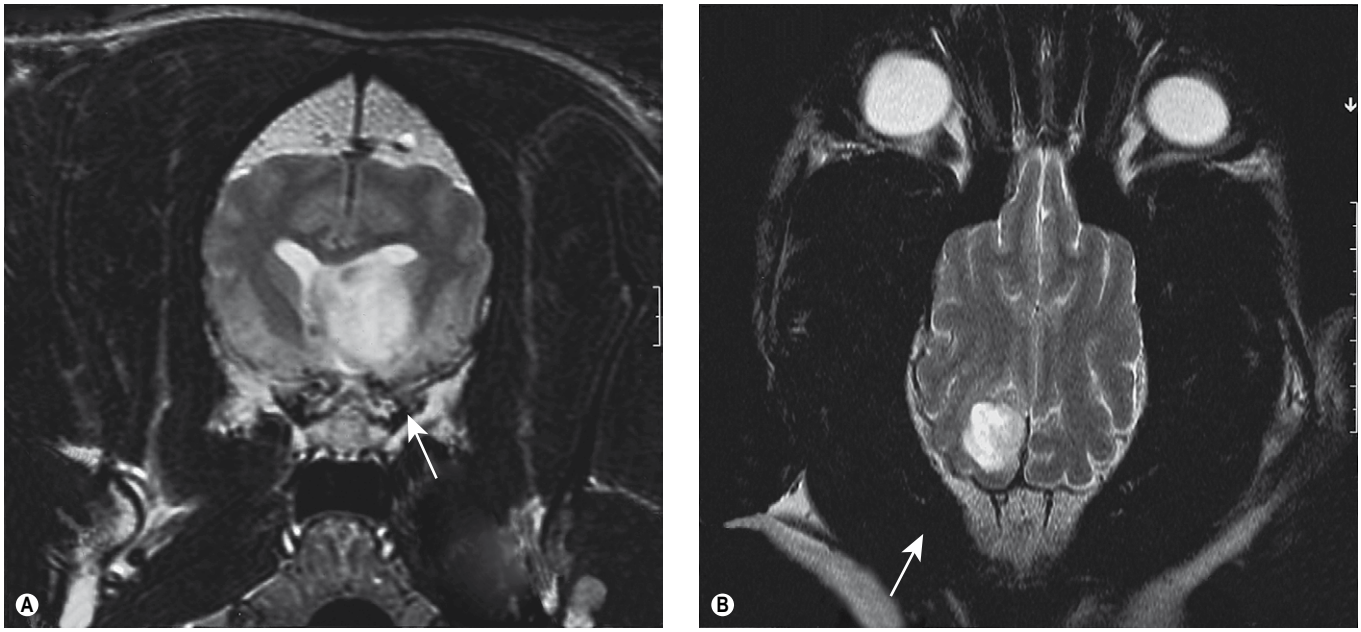

Figure 24.1 (**A**) T2-weighted transverse MRI scan showing a large hyperintense mass consistent with a glioma. (**B**) T2-weighted horizontal MRI scan of a large hyperintense mass (meningioma).

change being inflammatory. A neutrophilic pleocytosis has been associated with meningiomas (Bailey & Higgins 1986) but was not found to be a typical finding in another study (Dickinson et al 2006). The greatest elevations in CSF total protein were associated with choroid plexus tumours (Bailey & Higgins 1986). In patients with lymphoma, neoplastic cells may be identified. The value of CSF analysis is to rule out inflammatory and infectious causes of cerebral dysfunction rather than diagnose a brain tumour. Nevertheless, CSF analysis may support the diagnosis of a tumour; however, if a tumour is suspected, sampling should be taken after the MRI/CT scan as increased intracranial pressure may lead to brain herniation.

Differential diagnoses include vascular disorders (vascular accidents), trauma, immunological (e.g. granulomatous meningoencephalitis, GME), infection (e.g. protozoal), toxicity, degeneration, congenital or idiopathic (epilepsy).

MRI/CT characteristics of brain tumours

Meningiomas are usually broad-based, peripherally located and show uniform enhancement with contrast agent (Troxel et al 2004, Turrel et al 1986a).

Glial tumours typically are centrally located with ring-like, non-uniform enhancement and poorly defined margins (Kraft et al 1997, Troxel et al 2004, Turrel et al 1986a).

Choroid plexus tumours are well-defined, hyperdense masses with uniform contrast enhancement (Turrel et al 1986a).

Pituitary tumours are located at the sella turcica, have little peritumoral oedema and extend dorsally with uniform contrast enhancement and well-defined margins (Turrel et al 1986a).

Biopsy

The majority of brain tumours are 'diagnosed' based on the MRI/CT image, primarily because of the concerns about the risks of obtaining an ante-mortem diagnosis in a veterinary patient. If a histological diagnosis is obtained it is usually an excisional biopsy acquired if the tumour is considered resectable based on imaging studies. CT-guided stereotactic biopsy systems provide rapid and accurate means of obtaining a biopsy with a low complication rate; however, access to this technology is extremely limited and expensive.

Treatment options for canine brain tumours

Initial treatment

In all patients with primary brain tumours it is essential to control the secondary effects of the tumour, e.g. peritumoral oedema, seizures and increases in ICP pressure. Steroids are indicated to reduce oedema; in the seizuring patient anticonvulsant therapy should be started (phenobarbital or potassium bromide).

Medical management

For patients treated symptomatically only, survival times are in the range of 2–3 months. In one study the median survival time (MST) was only 6 days (Heidner et al 1991) for dogs with no treatment or symptomatic treatment. Obviously the overall survival time in an individual depends on a number of factors: type of tumour (patients with meningiomas may live longer as these tumours are slow growing), location within the brain, associated clinical signs and the ease with which they can be controlled, and the general health of the patient.

Surgery

Surgical options include complete removal, partial removal or biopsy. In dogs, meningiomas are more invasive than their feline counterparts but long-term survival with surgery, either as primary treatment or in combination with radiotherapy, has been reported. In one study, dogs treated with surgery alone had an MST of 198 days with a 1-year survival rate of 30% (Niebauer et al 1991). Survival times in excess of 2 years have been reported with combinations of surgery and radiotherapy (Heidner et al 1991).

In 31 dogs with intracranial meningiomas, those that underwent tumour resection alone and survived >1 week after surgery had an MST of 7 months (range 0.5–22 months). Dogs that underwent tumour resection followed by radiotherapy had an MST of 16.5 months (range 3–58 months) (Axlund et al 2002). Twenty dogs with incompletely resected intracranial meningiomas were treated with adjuvant radiotherapy and the 2-year progression-free survival was 68% (Théon et al 2000).

Removal of neoplasms in the caudal fossa and brain stem involves significant morbidity and mortality, and are better treated with other forms of therapy such as radiotherapy and/or chemotherapy. Calvarial tumours such as osteosarcoma, chondrosarcoma and multilobular osteochondrosarcoma (MLO) may be treated with surgical excision successfully (Dernell et al 1998) (see Chapter 21). Surgical debulking and adjuvant radiotherapy has been described as a treatment option for MLO (Dernell et al 1998, Straw et al 1989).

Greco et al (2006) reported on the use of a surgical aspirator to resect intracranial meningiomas in 17 dogs. Better outcomes were achieved than with traditional surgery alone or surgery and radiotherapy, or radiotherapy alone. The MST was 1254 days. Histological subtype of the tumour was prognostic (anaplastic, 0 days; fibroblastic, 10 days; psammomatous, >313 days; meningothelial, >523 days; transitional, 1254 days).

Radiotherapy

The treatment of choice for the majority of patients with a brain tumour is radiotherapy (Bley et al 2005, Evans et al 1993, LeCouteur et al 1987, Turrel et al 1986b). In one study (Bley et al 2005) 46 dogs with brain tumours were treated with a fine fractionated protocol (2–4 Gy/fraction to a total dose of 35–52 Gy) had on MST of 1174 dogs. In contrast, Brearley et al (1999) repeated survival times for dogs treated with a hypo-fractionated protocol (streatments once weekly to a total dose of 41 Gy) of 49. 7 weeks for extra-avoid ones. As the majority of these tumours are large when first diagnosed, it is important that these patients are referred early to a facility equipped to treat them. The more compromised the patient, the poorer the prognosis, and as access to MRI and CT is becoming routine, making diagnosis easier and facilitating treatment as soon as possible, this will contribute to improve survival times as will the development of better treatment protocols. The authors advise prioritizing patients with brain tumours because of how quickly they can destabilize.

Side effects from radiotherapy treatment Normal brain tissue is relatively resistant to the effects of radiotherapy, however, as with any treatment side effects can occur.

- *Acute*: These occur during or shortly after radiotherapy and are due to radiation-induced oedema. Initially, this may cause a mild increase in neurological signs;

however, it is self-limiting and to minimize this patients undergoing radiotherapy for brain tumours can be given anti-inflammatory doses of prednisolone.

- *Early-delayed*: Early-delayed effects result from temporary demyelination caused by the effects of radiation on oligodendroglial cells or radiation-induced changes in vascular permeability. Early vascular abnormalities and tumour necrosis may induce clinical and radiographic signs that cannot be distinguished from tumour progression. Treatment is steroid therapy as required.
- *Late-delayed*: These effects, should they be seen, are potentially more serious; however, they are not seen until many months to years after treatment and will present as focal or diffuse damage to the white matter. The presentation depends on the extent of the damage and the exact location. This is attributed to vascular injury or to a direct effect on glial cells.

The actual tolerance of the brain depends on the total dose of radiation given and the dose/fraction. In the majority of patients treated with radiotherapy, as this is palliative therapy only, the recurrence of clinical signs due to tumour progression is more frequently seen than any late-delayed effects of treatment.

It should be noted that any patient whose initial clinical sign is seizures might require anticonvulsant therapy for the remainder of their life. Once a seizure focus has formed, then even with successful treatment of the underlying tumour, the patient may continue to have seizures if not on anticonvulsants. The authors recommend continuing anticonvulsant medication for at least 6 months after treatment. If at that time no seizures have occurred, it can be slowly withdrawn.

Chemotherapy

In humans, metastases to the CNS occur in ~25% of patients with systemic neoplasms. In veterinary patients the incidence appears to be low but this may be underestimated and the longer survival times that we now see in our veterinary patients may lead to more CNS metastases being recognized. The blood–brain barrier (BBB) limits entry of tumour cells into the brain, the exception being lymphoid tumours as lymphocytes can cross the BBB. However, it is thought that brain tumours may compromise the BBB and allow chemotherapy to access the tumour. Dogs with glial cell tumours and meningiomas may respond partially to lomustine and prednisolone (Jung et al 2006), or carmustine (Dimski & Cook 1990), or lomustine alone (Fulton & Steinberg 1990).

Metastatic disease to the CNS has a poor prognosis, and although radiotherapy can be considered as a palliative, this has not been widely reported.

CNS lymphoma overall carries a poor prognosis. Whole brain radiation will produce short-term control but in general CNS lymphoma is an aggressive tumour with a predilection for the leptomeninges.

Tumours of the spinal cord

Primary tumours of the spinal cord are seen infrequently in dogs and are classified as extradural (50%), intradural–extramedullary (30%) or intramedullary (15%) (Wright 1985). The median age is 10 years, with 30% of tumours occurring in patients less than 3 years of age (Luttgen et al 1980). The primary spinal cord neoplasm seen most frequently in young dogs is neuroepithelioma (Moissonnier & Abbott 1993). Ninety per cent of spinal cord tumours occur in large breed dogs (Luttgen et al 1980).

- Extradural tumours are usually primary malignant bone tumours (OSA, CSA, FSA, HSA, haemangioendothelioma, myeloma) and tumours metastatic to bone and soft tissue (Wright 1985)
- Intradural–extramedullary lesions are mostly meningiomas and peripheral nerve sheath tumours (Wright 1985). Meningiomas are the most commonly diagnosed primary spinal cord neoplasm in dogs. Fourteen per cent of canine CNS meningiomas involved the spinal cord, with the cervical cord most frequently affected (40% cervical, 32% thoracic, 28% lumbar) (Luttgen et al 1980). Peripheral nerve sheath tumours (PNSTs) also affect the spinal cord (Fingeroth et al 1987, Wright 1985). Neuroepithelioma (ependymoma, medulloepithelioma, nephroblastoma and spinal cord blastoma) is seen in young dogs (6 months to 3 years of age), especially German Shepherds and Retrievers. It has a predilection for T10–L2 spinal cord segments (Blass et al 1988, Ferretti et al 1993, Moissonnier & Abbott 1993, Ribas 1990, Summers & deLahunta 1986, Summers et al 1988, Tamke & Foley 1987).
- Intramedullary spinal tumours of dogs occur infrequently and are mostly of glial cell origin. Granulomatous meningoencephalitis (GME) may also affect the spinal cord. Metastatic lesions of HSA and lymphoma have a tendency for intramedullary spinal cord involvement (Waters & Hayden 1990). HSA is the most common secondary tumour affecting the canine spinal cord.

History and clinical signs

Extramedullary tumours are often slow growing, gradually resulting in spinal cord compression (weeks or months), but can show an acute onset of signs and are often painful. Intramedullary lesions tend to grow quickly, causing necrosis, ischaemia or haemorrhage, and corresponding rapid neurological dysfunction, without apparent pain.

Intradural–extramedullary tumours frequently have prolonged, intermittent signs. They are usually not painful until advanced and signs are often lateralized for PNST. Isolated plasmacytomas have also been identified.

Brachial or lumbar intumescence tumours may show lameness, root signature, muscle wasting and lower motor neuron (LMN) signs to the affected limb (see below).

Diagnostic workup

This comprises physical examination (including a neurological examination to localize the affected segment of the spinal cord), haematology, biochemistry, thoracic radiographs for primary or metastatic neoplasia, radiographs of vertebral column (best under general anaesthesia), CSF tap, myelography or advanced imaging (CT/MRI), and very occasionally a biopsy of the lesion.

Radiography

Primary or secondary vertebral tumours may produce bone lysis, new bone production or both. The vertebral body and

arch are more often affected than dorsal spinal processes or transverse processes. Expansion of a spinal tumour may result in enlargement of an intervertebral foramen, widening of vertebral canal or thinning of surrounding bone.

CSF analysis

Lymphoma often results in an elevated white cell count that consists of predominantly abnormal lymphocytes (Lane et al 1994, Spodnick et al 1992).

Myelography

Myelography is a useful tool in the diagnosis of spinal cord neoplasms; however, it causes an inflammatory change in the CSF for up to 3 weeks so it is important to collect CSF before injection of contrast agent. Neurological function is often worse for 12–24 hours after myelography and the patient should be monitored closely for seizures that may occur after injection of contrast.

Advanced imaging

CT is useful for bone detail. CT and MRI are non-invasive and provide images preferable to radiography/myelography.

Biopsy

Surgical biopsy is usually not carried out due to morbidity, and often a presumptive diagnosis and therapeutic plan are made after a thorough work-up.

Treatment

The immediate goal is to relieve the deleterious effects of sustained spinal cord compression. Hemilaminectomy is the treatment of choice and, depending on the histological diagnosis, radiotherapy and/or chemotherapy may be indicated.

- *Lymphoma*: radiotherapy and chemotherapy.
- *Isolated plasmacytomas*: surgery and/or radiotherapy.
- *Extradural sarcomas*: palliative radiotherapy for bone pain; depending on neurological dysfunction, surgical decompression.
- *Meningiomas*: slow growing and can often be completely removed surgically with a good prognosis (Levy et al 1997). Adjuvant radiotherapy has been shown to increase survival times in patients with incompletely resected spinal cord tumours up to 20 months (Siegel et al 1996).
- *Nerve sheath tumours*: once the spinal cord is compromised, complete surgical removal may be difficult, and although adjuvant radiotherapy may help prolong the disease-free interval (Siegel et al 1996), the number of cases that have been managed is small.

Prognosis

Prognosis depends on resectability, histological type, and location and severity of clinical signs. Generally, dogs and cats with an extradural metastatic tumour or vertebral tumour have a poor prognosis and palliative therapy only is attempted. Removal of affected vertebrae may be (rarely) possible.

Spinal meningiomas may be completely resected with a good prognosis. Survival times in excess of 6 months after surgical removal have been reported (Fingeroth et al 1987). CNS lymphoma may occur as a primary extranodal form (Dallman & Saunders 1986) but is more commonly part of multicentric lymphoma. Intrathecal chemotherapy, systemic chemotherapy and irradiation have been tried (Couto et al 1984). Several cases of ependymoma and lymphoma treated with radiotherapy have resulted in alleviation of clinical signs for greater than 1 year (LeCouteur & Withrow 2007).

The MST for spinal nerve sheath tumours was 180 days (Levy et al 1997) when treated with surgery. Levy reported 37 dogs with spinal tumours, 23 of which died or were euthanized within 20 days of diagnosis. The MST of the 22 dogs (treated with surgery ± adjuvant therapy) followed >20 days after diagnosis was 240 days. Overall, the MST was 1410 days for benign, compared to 180 days for malignant tumour types (Levy et al 1997).

Brehm et al (1995) reported an MST of about 5 months after surgical treatment of PNST of the nerve root.

Tumours of the peripheral nervous system

Primary peripheral nerve tumours may affect cranial nerves, peripheral nerves, sympathetic nerves and ganglia, and nerves of the adrenal glands.

Peripheral nerve sheath tumour

The most common primary malignant tumour of the peripheral nervous system is the peripheral nerve sheath tumour (PNST). PNST may affect the spinal nerve roots (and can invade the vertebral canal as mentioned above), the brachial or lumbar plexus, and/or the peripheral nerves distal to the lumbar or brachial plexus (Brehm et al 1995). In one study, the distribution of PNSTs showed that a significant number involved spinal nerves (39/60), with 17/60 involving peripheral nerves and only 4/60 involving the cranial nerves. Males were over-represented with an age range of 2–17 years (Bradley et al 1982).

Of 40 dogs with tumours of the brachial plexus, 20 had spinal cord invasion, 4 had tumour arising primarily in the dorsal root, within the vertebral canal, and 16 had tumour arising in a peripheral nerve and invading the spinal cord late in the course of disease. Survival times of dogs with nerve sheath tumours have been reported as 10 days to 92 months, with more peripheral tumours tending to have a better prognosis with surgical treatment (Brehm et al 1995).

When PNSTs affect the cranial nerves, the vestibulocochlear and trigeminal nerves are most commonly involved, although oculomotor or other cranial nerves can be affected.

Lymphoma

Lymphoma is the most common secondary tumour to the cranial and spinal nerves and nerve roots of dogs (Hobbs & Cobb 1990, Pfaff et al 2000, Rosin 1982).

Paragangliomas and neuroblastomas

PNS tumours arising from the sympathetic nervous system (paragangliomas and neuroblastomas) most commonly show invasion and metastasis.

Paragangliomas (phaeochromocytomas and chemodectomas) are tumours of the peripheral (autonomic) nervous system. Most phaeochromocytomas arise from the chromaffin cells within the adrenal medulla, but a few arise from chro-

maffin cells of the sympathetic ganglia (which have not regressed normally), and have instead become sites of tumour formation. Chemodectomas are non-chromaffin paragangliomas, which can occur at the aortic body (heart base) or the carotid body (neck).

Neuroblastomas are rare malignant tumours, otherwise known as primitive neuroectodermal tumours, composed of primitive neuroepithelial cells and arising from the sympathoblasts of the sympathetic nervous system. They can be tumours of the CNS or PNS (e.g. neuroblastoma, medulloblastoma and retinoblastoma). In dogs, neuroblastomas have been reported as large masses in older dogs (Capucchio et al 2003, Ueno et al 2007), as well as disseminated disease or a localized mass in young dogs (Forrest et al 1997, Kuwamura et al 2004, Marcotte et al 2004, Matsushima et al 1998, Suzuki et al 2003).

Further information regarding phaeochromocytomas and chemodectomas is discussed in Chapter 26. Neuroblastomas can occur anywhere in the CNS or PNS, so clinical signs are dependent on their location(s) and extent of disease. There is limited information on the survival of dogs with neuroblastomas, although it appears that young dogs have a grave prognosis (Forrest et al 1997, Kuwamura et al 2004, Matsushima et al 1998, Suzuki et al 2003) and older dogs with localized disease can respond to treatment (Ueno et al 2007).

History and clinical signs

For cranial nerve PNSTs, clinical signs are localizable to deficit(s) of the particular cranial nerve(s) affected. For PNSTs of the brachial plexus, clinical signs shown are commonly unilateral thoracic limb lameness and muscle atrophy (Brehm et al 1995). Other signs that may be seen include pain (particularly with abduction of the affected forelimb), a palpable axillary mass, Horner's syndrome (with involvement of C6–T2 spinal segments), LMN signs to the affected limb, and signs of cervical spinal cord compression (generally as a late event) (Bradley et al 1982).

Signs of a PNST involving the lumbosacral plexus are progressive lameness of a hind leg and muscle atrophy, with pain a less consistent finding (Bradley et al 1982). Urinary or faecal incontinence may be present if the PNST has invaded the spinal canal and the contralateral limb may eventually be invaded also (Bradley et al 1982). PNSTs are usually slow-growing tumours, with associated clinical signs progressing over weeks to months. Lymphoma affecting the peripheral nervous system may be indistinguishable from a PNST based on clinical signs (LeCouteur & Withrow 2007), although nerve sheath lymphoma is often part of multicentric disease.

Diagnostic work-up

For diagnostic evaluation for multicentric lymphoma, see Chapter 22. For extranodal lymphoma of the PNS, diagnosis is based on clinical signs, imaging and cytology/histopathology.

The diagnosis of PNST is based on clinical signs and an incisional biopsy or fine needle aspirate (FNA) cytology if there is any externally accessible, palpable mass. This is mainly to rule out other tumours such as lymphoma, which would not be treated surgically. PNSTs are known by a variety of names (malignant PNST, schwannoma, neurofibroma, neurofibrosarcoma, Schwann cell tumour, etc.). These tumours do not behave in a benign fashion despite a histologically benign appearance and low metastatic potential. Cases of trigeminal nerve sheath tumours not treated showed a progressive course, eventually resulting in euthanasia or death (Bagley et al 1998).

Other tests which may aid in the diagnosis include plain radiographs (may reveal widening of the intervertebral foramen(a), where the nerve root has gradually remodelled the surrounding bone), electromyelography (EMG), nerve conduction velocity studies, mapping of cutaneous sensation, and advanced imaging (contrast-enhanced CT/MRI and myelography). These may all help localize a PNST to a specific sensory or motor nerve, to a plexus, or to a group of spinal nerves or nerve roots. A thorough neurological examination and advanced imaging (CT/MRI) are needed for PNST (or lymphoma) of the cranial nerve(s).

PNSTs appear as nodular or varicose thickenings of large nerves, often with an associated palpable mass (e.g. in the axilla for brachial plexus PNSTs). However, at an early stage these tumours can be hard to diagnose, even with advanced imaging such as contrast-enhanced CT and MRI, and surgical exploration and biopsy may be the only way of definitively obtaining a diagnosis.

CSF analysis is not expected to help diagnose a PNST (sarcoma cells rarely exfoliate readily), although elevated CSF protein may be found.

CT/MRI are preferable to myelography or plain radiographs for identifying PNST proximity to the spinal cord, and may identify which patients are no longer surgical candidates, due to spinal cord invasion (**Figure 24.2**).

Treatment

PNSTs are a kind of soft tissue sarcoma (STS), but behave in a different manner to more 'typical' subcutaneous STS (see Chapter 20). PNSTs tends to grow up and down the length of the nerve(s) involved and can distort the architecture of the nerve with multiple nodular thickenings of various sizes, often forming mass(es). However, the 360-degree microscopic tentacles of invasion into surrounding tissue and along fascial planes (seen with 'typical' subcutaneous STS) are not normally seen in the authors' experience. Surgically this is important,

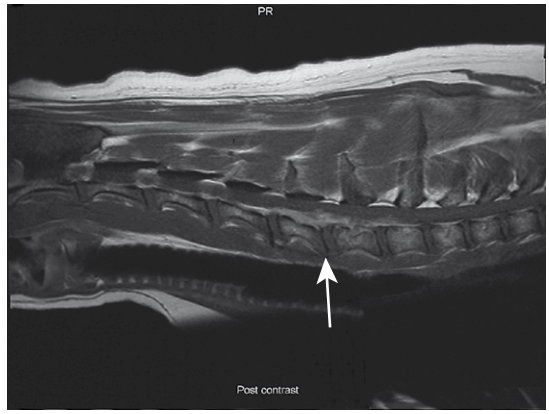

Figure 24.2 Sagittal MRI scan showing invasion of spinal cord from a peripheral nerve sheath tumour.

as curative surgical excision can be achieved with removal of all nerve(s) involved rather than all nerves involved and a wide (360 degree) margin of grossly normal tissue. However, it is still important to obtain a wide margin (3 cm if possible) of grossly normal peripheral nerve tissue proximal (and distal) to the PNST. Severed ends of the nerve(s) should be inked or sutured and the pathologist should assess these margins for completeness of excision.

Surgical excision in the vast majority of plexus tumours necessitates limb amputation, as the limb cannot function without its nerve supply. Complete excision is impossible if there is proximal extension of tumour into spinal cord. However, if there does not appear to be spinal cord involvement on preoperative CT/MRI (preferable) or myelography, a curative surgical excision with clean margins should be attempted. A laminectomy and durotomy may be needed to obtain an adequate margin of normal tissue between tumour and spinal cord. Postoperative radiotherapy may prolong the disease-free interval for incompletely resected PNST, but there are no published reports on this.

For PNST of the cranial nerves where surgery is not an option, radiotherapy may be the only treatment likely to improve survival times. Chemotherapy may be of palliative benefit, but due to the location, slow progression and usually late diagnosis, is unlikely to impact on survival times.

Lymphoma of peripheral nerves is treated with chemotherapy or radiotherapy (as for CNS lymphoma).

Prognosis

The overall prognosis for PNSTs is poor, and the recurrence rate after surgical treatment is high (Brehm et al 1995); this is likely due to incomplete resection as a result of proximal extension of tumour close to spinal cord. Intuitively, dogs with nerve sheath tumours affecting a nerve peripheral to a plexus have a better prognosis with surgical resection than dogs with tumours affecting a plexus or invading the spinal canal. One dog survived 3 years after surgical excision of a PNST of the sixth cervical spinal nerve (Budzilovich 1968). Late metastases to the lungs have been reported infrequently (Bagley et al 1998).

Neurological complications of systemic cancer

Cancer arising outside the nerve sheath can have direct and indirect effects on the nerve sheath but are probably underreported in veterinary medicine. These would include metastatic lesions from extracranial neoplasms to the brain, spinal cord or nerve roots. Other possible effects include metabolic encephalopathy due to the failure of cerebral metabolism because of systemic illness, e.g. electrolyte imbalance, hepatic or renal failure, hypoxia, sepsis. CNS infections lead to altered immune mechanisms or neutropenia secondary to cancer or cancer therapy. Coagulopathies lead to an increased risk of cerebrovascular complications. Embolic infarction may occur secondary to endocarditis or sepsis. Neurological complications can arise from cancer treatment, e.g. radiation or chemotherapeutic agents. Paraneoplastic syndromes include sensorimotor polyneuropathy, myasthenia gravis (associated with thymoma) and polymyositis.

TUMOURS OF THE FELINE CNS

Brain tumours

The most common intracranial neoplasm seen in the cat is meningioma (58% of feline intracranial neoplasia in one study of 160 cases) (Troxel et al 2003), with older male cats being more susceptible (66% of cats ≥10 years old) (Nafe 1979). Lymphoma was the second most common feline intracranial neoplasia (14%), followed by pituitary tumours (9%) and gliomas (7.5%) (Troxel et al 2003). CNS lymphoma may be either primary or secondary. Forty percent of 28 cats with primary renal lymphoma developed CNS disease, even with treatment (Mooney et al 1987). Multiple tumours are frequently reported (Forterre et al 2007, Gordon et al 1994, Nafe 1979, Troxel et al 2003).

Tumours of the ear, nasal cavity and calvarium (**Figure 24.3**) may invade into or impinge onto brain. Seventy per cent of feline brain tumours are primary, only about 6% are metastasic, and only about 4% are from direct extension of secondary tumours (Troxel et al 2003). Pituitary macroadenomas are discussed in Chapter 26. Tumour location was predictive of tumour type in one study, with diffuse cerebral or brain stem involvement predictive of lymphoma and third ventricle involvement predictive of meningiomas (Troxel et al 2003).

Clinical signs

Clinical signs in the feline patient with intracranial neoplasia are similar to that of the canine patient. The most common presenting sign in dogs is seizures, whereas in cats, the most common neurological signs are altered consciousness (26%), circling (23%) and seizures (23%). Cats without specific neurological signs are common (21%), and incidental finding of tumour occurred in about 19% of cats (Troxel et al 2003). In another study of 61 cats with intracranial neoplasia, 23% had a history of seizure(s) and 77% had no history of seizure(s) (Tomek et al 2006).

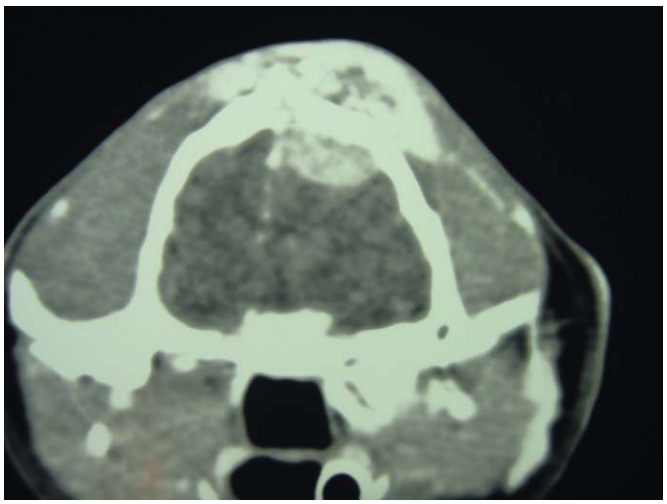

Figure 24.3 Contrast-enhanced osteosarcoma of the calvarium in a cat with extension into the underlying brain.

Diagnostic work-up

The diagnosis of lymphoma in cats is often presumptive, based on feline leukaemia virus (FeLV) positive status, clinical signs and leukaemic bone marrow (Spodnick et al 1992). Otherwise, diagnostic work-up is similar to the canine patient.

For a patient with clinical signs consistent with a brain tumour, an MRI scan is indicated.

Treatment

The best candidates for brain surgery are cats with superficial or olfactory meningiomas. Feline meningiomas are not locally invasive, do not metastasize, rarely recur locally, and can be consistently cured with surgery. They are usually removed via craniotomy (**Figure 24.4**), with a high overall success rate. However, the location is important, and for tumours located in the caudal fossa or brain stem, surgery causes significant morbidity and mortality. A number of studies have evaluated the long-term survival of cats after craniotomy (Forterre et al 2006, Gallagher et al 1993, LeCouteur 1999) with overall survival times of approximately 66% at 1 year and 50% at 2 years (Gordon et al 1994). Median survival times of 485 days and 27 months have been reported following surgery (Gallagher et al 1993, Niebauer et al 1991). For those tumours suitably located for surgery, the major prognostic indicators include duration of clinical signs and size of tumour. Distant metastasis is extremely rare.

There are few reports on radiation and feline brain tumours primarily because the majority of tumours are superficial meningiomas that one treated surgically. For those patients not amenable to surgery radiation should be considered. The most common feline brain tumour treated with radiation is lymphoma.

Cats with intracranial lymphoma tend to be younger than cats with meningiomas (Tomek et al 2006). In one large study, lymphoma of the CNS accounted for up to 12% of patients with lymphoma (Lane et al 1994). Treatment comprises whole brain radiation and chemotherapy that includes drugs which penetrate the blood–brain barrier, e.g. prednisolone, cytarabine arabinoside.

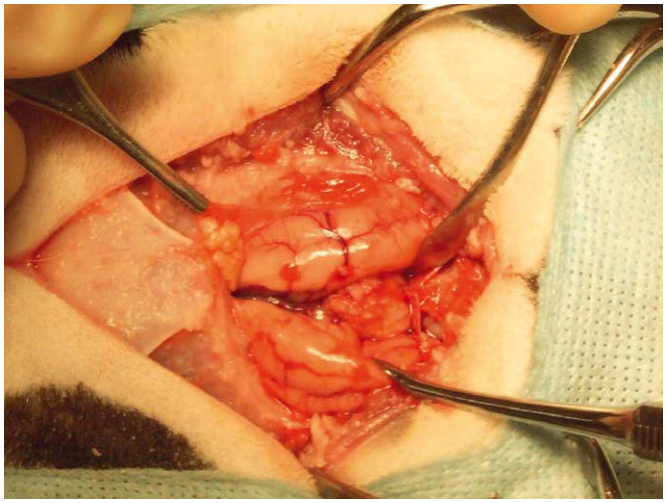

Figure 24.4 Craniotomy in a cat.

Pituitary macroadenomas

See Chapter 26.

Tumours of the spinal cord

- *Extradural*: lymphoma is the most common tumour of the spinal cord, either primary or secondary, and shows a predilection for thoracic and lumbar regions (Lane et al 1994); 81% of cats present with hind limb weakness. Eighty-five per cent of cats presenting with neurological signs had multicentric disease at necropsy (Spodnick et al 1992). Eighty-four per cent of cats with spinal lymphoma were FeLV positive in one study (Spodnick et al 1992), and 94% in another (Lane et al 1994). Feline spinal lymphoma occurs in young FeLV-positive cats (which often have lymphoma elsewhere) (Spodnick et al 1992) and in older, usually FeLV-negative cats. OSA is also seen. Single or multiple osteochondromas are reported but are uncommon.
- *Intradural–extramedullary*: meningiomas (uncommon).
- *Intramedullary*: rare.

Treatment

Treatment of lymphoma consists of radiotherapy and chemotherapy. Median remission time in cats treated with chemotherapy is about 14 weeks (Spodnick et al 1992). Spodnick also reported a single cat treated by laminectomy and postoperative chemotherapy, which had a prolonged remission (62 weeks).

Tumours of the PNS

PNSTs are reported infrequently in cats, but solitary nerve sheath tumours may be seen in this species (Hoffman et al 2005, Jones et al 1995, Okada et al 2007, Tremblay et al 2005).

Lymphoma has been reported in the cranial and peripheral nerves of cats (Allen & Amis 1975, Schaer et al 1979).

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Tumours of the eye and retrobulbar space

Eyelid tumours

Canine

Most commonly benign, eyelid tumours are usually seen in older dogs. Complete excision with narrow margins is curative for sebaceous gland adenoma/Meibomian gland tumour, benign melanoma and squamous papilloma. Papillomas tend to be well circumscribed, superficial with minimal invasion of deeper tissues, and commonly resolve spontaneously. Histiocytomas occur in young to middle-aged dogs, and in young dogs often resolve spontaneously. Roberts et al (1986) reported that 88% of eyelid neoplasms in dogs were sebaceous tarsal gland adenomas, benign melanomas or papillomas, and that malignant tumours (melanoma, adenocarcinoma, basal cell carcinoma, mast cell tumour, squamous cell carcinoma, haemangiosarcoma and myoblastoma) comprised only 8.2%. Other malignant eyelid tumours in dogs include lymphoma (LSA) and fibrosarcoma (FSA).

Feline

Eyelid tumours in cats are less common than in the dog but are more often malignant (Aquino 2007). Most commonly they tend to be squamous cell carcinoma (SCC), mast cell tumour (MCT) or LSA (see relevant chapters). Other tumour types occur rarely.

Treatment

Surgery

For malignant tumours of the eyelid, it is more important to achieve wide clean margins than to achieve perfect eyelid reconstruction. However, the eyelid must be able to function so as to maintain ocular health. Sutures should be buried so as not to irritate the cornea. Enucleation of the eye or exenteration of the orbit may be necessary to allow a curative resection. The usual principles of oncology should be adhered to (e.g. staging prior to surgery, removal of enlarged regional lymph nodes at surgery for staging purposes and assessment of inked surgical margins to ascertain histological margin).

Techniques to reconstruct the eyelid have been reported in both dogs and cats. Lesions involving one-quarter to one-third of the eyelid margin can be reconstructed with a simple V-plasty (wedge excision). Electrosurgery is not recommended but CO_2 laser works well (Bussieres et al 2005). A lip-to-lid flap has been used successfully to replace lower eyelid defects in cats (Hunt 2006). Split eyelid flaps can also be used in dogs and cats (Hagard 2005, Lewin 2003). A cross-lid flap method has also been described (Munger & Gourley 1981). Other techniques, such as reverse triangles, H-plasties and rotation flaps, are also reported (Stades 1987), along with use of the third eyelid as part of eyelid reconstruction with transposition flaps. Free hard palate mucosal grafts have also been used with success in dogs to replace eyelid deficits (Zhao & Li 1996).

Hoffman et al (2005) reported six cats (from a database of 3997 feline ocular histopathology submissions) with a histological diagnosis of peripheral nerve sheath tumour arising from the eyelid or conjunctiva. All cats treated with surgical excision, cryoablation or laser ablation had an average of three recurrences of the tumour, whereas two-thirds of those treated with wide excision had no recurrence (Hoffman et al 2005).

SCC of the eyelid is common in cats with repeated exposure to UV light and poorly pigmented skin (similar to SCC of the nasal planum and pinnae in cats, see Chapter 18) (**Figure 25.1**). Early stages may be confused with chronic conjunctivitis. Surgical resection with adequate margins is often curative as there is a low rate of metastasis (10–15%).

Radiotherapy

Radiotherapy may be used for tumours with known radiation responsiveness, such as LSA and SCC. However, LSA is often treated with chemotherapy and larger SCCs are better treated with surgery than radiotherapy. Side effects of radiation include erythema, alopecia, leukotrichia, keratoconjunctivitis sicca, keratopathy, uveitis and cataract.

Chemotherapy

Rarely used for eyelid neoplasms in dogs and cats, chemotherapy may be indicated for LSA or MCT of the eyelid (see Chapters 19 and 22).

Third eyelid and conjunctival tumours

The differential diagnosis in cats and dogs includes SCC, papilloma, haemangioma, haemangiosarcoma (HSA), adenoma, adenocarcinoma, malignant melanoma (MM), MCT, LSA, and FSA. A pseudoneoplastic hypertrophy of the gland of the third eyelid may also occur. Prolapse of the gland of the third eyelid ('cherry eye') can usually be differentiated from neoplasia, because neoplasia (adenocarcinoma of the gland of the third eyelid) occurs primarily in older dogs (10–16 years). Fibrous histiocytomas (nodular granulomatous episcleritis) can also occur on the third eyelid.

Canine

Solar radiation appears to be a predisposing factor for the development of SCC (Hargis et al 1978). In humans, conjunc-

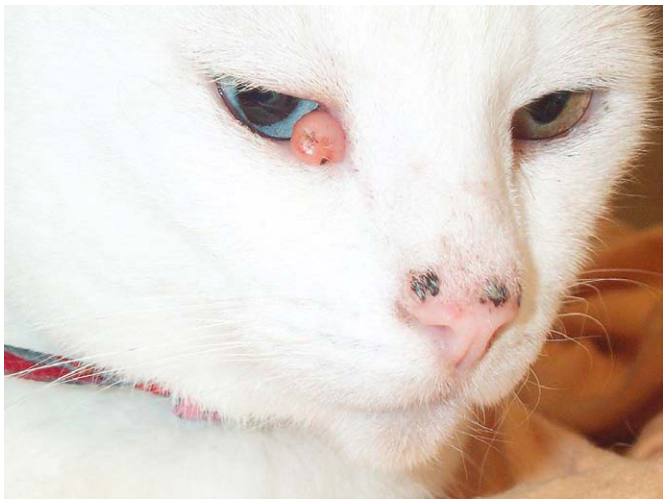

Figure 25.1 Squamous cell carcinoma in a cat. (Courtesy R Straw.)

Figure 25.2 Subconjunctival mast cell tumour in a dog.

tival scrapings are useful for in-house diagnosis (Spinak & Friedman 1977). This may also be the case for animals.

- *Papillomas* are benign and excisional biopsy is advisable (Bonney et al 1980).
- *Adenocarcinomas* of the gland of the third eyelid can be invasive. Metastasis (to the regional lymph nodes and orbit) is not a common feature, but is known to occur. They generally appear as a smooth, pink nodule on the bulbar aspect of the third eyelid. They have a good prognosis with early, adequate treatment, but recurrence is expected with incomplete excision. In order to give the best chance of complete excision, the entire third eyelid should be removed, and the eye should be enucleated if involved (Wilcock & Peiffer 1988).
- *Malignant melanoma* of the conjunctiva in dogs can be aggressive, with local recurrence after excision reported in 6/12 cases and metastasis in 2/12 cases (Collins et al 1993). Local treatment should be aggressive, with wide surgical excision including orbital exenteration if necessary. A combination of wide surgical excision and cryosurgery can be used (Collins et al 1991). The prognosis in dogs is guarded. As in the cat, histological features (mitotic index, cell type, degree of pigmentation) are not good predictors of behavioural malignancy (Collins et al 1993).
- *Mast cell tumour*: mucocutaneous sites are generally thought to be a poor prognostic location for MCTs (Chapter 19). However, there is little reported information on the behaviour of conjunctival MCTs. One report of a dog with a rapidly progressive grade II conjunctival MCT had excisional biopsy (close margins) and adjuvant treatment with prednisolone and vinblastine, with no evidence of local recurrence or metastasis during a 29-month follow-up period (Barsotti et al 2007). Two other reported canine cases of subconjunctival MCT had a relatively benign course (Johnson et al 1988) (**Figure 25.2**).
- *Conjunctival LSA* in dogs and cats may be misdiagnosed as conjunctivitis, as it can present as a diffusely swollen and firm conjunctiva (usually unilateral) (**Figure 25.3**).

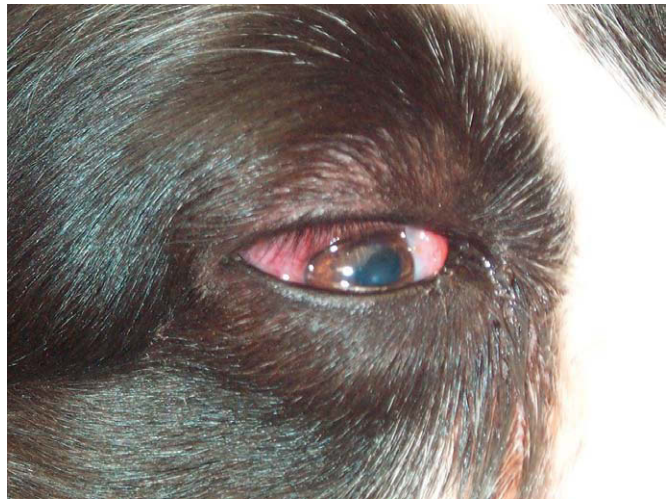

Figure 25.3 Conjunctival lymphoma in a dog.

For diffuse conjunctival swelling, an incisional biopsy under topical anaesthesia would be an appropriate diagnostic step (the author (TB) does not use sutures after an incisional biopsy, allowing healing by second intention). A conjunctival LSA in a dog (intermediate-grade, diffuse, large-cell lymphoma with T-cell immunophenotype) was treated with excisional biopsy. No adjuvant chemotherapy was given and there was no recurrence after 12 months.

- *Haemangioma and HSA*: Pirie et al (2006) evaluated 70 dogs with haemangiomas and 38 dogs with HSA. The average age was 8.6 years. Dogs with increased outdoor activity were predisposed. Most tumours occurred within non-pigmented epithelium along the leading edge of the nictitating membrane (41/108) and temporal bulbar conjunctiva (33/108). Ultraviolet light exposure was likely to be a significant risk factor. Early surgical resection with clean margins was thought to be curative. Local recurrence was more likely with HSA (11/20). In one case report (Liapis & Genovese 2004) of a dog with

HSA of the third eyelid, surgical excision with no other treatment showed no recurrence after 9 months.

Feline

- *Malignant melanoma*: in cats, conjunctival melanoma is usually malignant, with a high rate of early metastasis and a poor prognosis (Patnaik & Mooney 1988). An MM originating from the surface of the nictitating membrane reported in a 10-year-old cat infiltrated the orbital cavity causing exophthalmia, with metastasis to the cerebrum and the lungs (Roels & Ducatelle 1998). However, not all cases with histological features of malignancy have a poor prognosis. One case report (Cook et al 1985) reported complete excision of conjunctival MM without further evidence of local recurrence or metastasis during an 11-month follow-up period.
- *Conjunctival LSA*: see above comments for dogs. In cats, it is important to check feline leukaemia virus (FeLV) status, as many young cats with LSA are FeLV positive. There is a reported case of a cat with a conjunctival LSA with peripheral lymph node enlargement with Hodgkin's-like LSA (Holt et al 2006). The conjunctival swelling responded poorly to standard chemotherapeutic protocols for LSA, but responded well to radiation therapy, and had not recurred 3 years after treatment.
- *Haemangioma and HSA*: feline conjunctival haemangiomas and HSA were evaluated by Pirie & Dubielzig (2006). In all they looked at eight cases seen over a period of 9 years. Third eyelid location was the most common. In seven of eight cases, non-pigmented tissue was affected, and most had a history of high annual UV light exposure. Surgical excision with clean margins appeared to be curative. One case report of HSA of the third eyelid in a cat treated with surgery alone, had no recurrence after 7 months (Multari et al 2002).

Diagnostic work-up and staging

For suspected malignant tumours, fine needle aspirate (FNA) cytology or incisional biopsy is diagnostic. Ultrasound of the eye and periorbital tissues, CT or MRI is indicated if invasion is suspected. Thoracic radiographs (not generally needed for MCT) and abdominal ultrasound may be indicated in specific cases.

If staging is negative, a resection with curative intent is indicated. This includes removal of all the third eyelid for malignant tumours of the third eyelid, and exenteration of the orbit for malignant tumours that have invaded into the orbit. This deficit can be reconstructed with a caudal auricular axial pattern flap (Stiles et al 2003). Another paper has described wound reconstruction after radical orbital exenteration and tumour resection in six cases (Koch et al 1994). Excisional biopsy can be an appropriate first-line treatment for suspected benign disease (especially Meibomian gland adenomas).

Tumours of the external globe (cornea and sclera)

Melanoma of the limbus (the corneoscleral junction) is mostly benign in dogs (predisposition in German Shepherds) and cats, although malignancy and metastasis in cats is reported (Betton et al 1999, Day & Lucke 1995, Giuliano et al 1999). Solar radiation is thought to be a risk factor (Hargis et al 1978), because most occur at the superior limbal region. Surgical excision and cryosurgery is usually curative. However, limbal melanomas in older dogs may grow very slowly, and may be better observed than removed, although in younger dogs and in all cats they should be removed early. In older dogs, treatment is undertaken if there is rapid growth or invasion. Surgical excision and cryosurgery is usually curative.

Nd:YAG laser has been used in which 3 of 15 cats and dogs treated had recurrence (Sullivan et al 1996) (slightly higher than for combined excision and cryosurgery). Incomplete excision may result in slow local recurrence, but not metastasis (Wilcock et al 1986). Melanoma of the conjunctiva or third eyelid behaves more aggressively (see above) and must be differentiated from limbal melanoma. Intraocular tumours may extend into the limbus to mimic limbal melanoma, and examination of the iridocorneal angle (gonioscopy) is needed to rule this out.

Papilloma, histiocytoma, SCC, haemangioma, HSA (**Figure 25.4**), FSA, epithelioma and adenocarcinoma are uncommon tumours of the external globe.

A lump on the surface of the globe could also be immune-mediated nodular granulomatous episclerokeratitis (NGE) or necrotizing scleritis/keratitis, corneal/conjunctival cysts, foreign bodies, or globe perforation and iris prolapse. SCC of eyelid and conjunctiva can invade the cornea and sclera. Ocular LSA in dogs can invade the cornea, often causing haemorrhage. Infiltrating corneal lesions in dogs and cats may also resemble fibrous histiocytomas, which arise from the limbus. They show continuous growth, a benign appearance and a tendency to recur following excision keratoplasty, Collie dogs may be predisposed (Smith et al 1976).

Diagnostic work-up and staging

A high-frequency ultrasound probe allows tissue examination similar to low-power histology, but tissue penetration is limited to 5–10 mm, ideal for distinguishing between various anterior segment entities (e.g. anterior uveal tumours, iridociliary cysts and iris bombé) (Bentley et al 2003). Other investigations include:

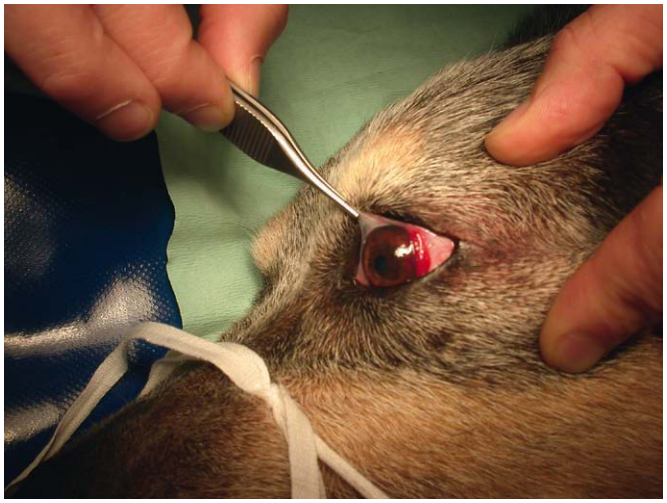

Figure 25.4 Scleral haemangiosarcoma in a dog. (Courtesy R Straw.)

- gonioscopy
- FNA cytology
- incisional biopsy
- abdominal ultrasound
- thoracic radiographs.

Treatment

Surgery

Surgical options include superficial keratectomy/sclerectomy, full thickness resection of cornea/sclera, and enucleation.

Cryosurgery may be useful for limbal SCC and limbal/epibulbar melanoma. Care should be taken not to damage intraocular tissues.

The use of laser for corneal surgery has been described (Gilmour 2003).

Transplantation of frozen canine amniotic membrane has been used successfully to reconstruct the cornea in dogs and cats (Barros et al 2005).

Porcine small intestinal mucosa grafts covered by a conjunctival flap can be used to repair full thickness corneal wounds in dogs and cats (Bussieres et al 2004).

Intraocular tumours

Animals with intraocular tumours (primary or secondary) may present with glaucoma, uveitis, ocular haemorrhage and retinal detachment, which may disguise the underlying tumour.

Melanoma in dogs

Melanoma is the most common primary intraocular tumour in dogs and cats. It arises from iris or ciliary body (anterior uveal tract), and is rarely choroidal. About 80% of intraocular melanocytomas and 95% of intraocular melanomas were found to arise in the anterior uveal tract. In dogs, intraocular melanoma tends to be benign, with a low rate of metastasis (5%), although they can still be locally invasive (Giuliano et al 1999). Mitotic index is suggested to be the best criterion for histological identification of ocular melanomas with high metastatic potential. Cell type or pattern of growth within the globe was not predictive of biological behaviour (Wilcock & Peiffer 1986).

In a series of 224 cases, tumour extension, tumour size and mitotic index were not found to be reliable predictors of survival. Dogs with MM had only a slightly decreased survival time compared to control dogs and dogs with melanocytomas. At the time of enucleation, most tumours invaded the sclera, but did not show extrascleral extension (Giuliano et al 1999). A worse prognosis was given in a study of 16 dogs with uveal melanomas, where 3 had metastasis within 3 months of enucleation. Benign melanomas tend to be darker and more heavily pigmented than MM (Wilcock & Peiffer 1986). Melanoma of the iris in dogs often appears as a discrete, brown nodule on the surface; however, it can be diffuse and can look like an iris cyst or benign iris melanosis.

Choroidal melanomas are rare (only 4% of canine uveal melanomas). Some remain static for many years; others invade the retina, sclera, optic nerve and orbit. One reported case of a 7-year-old Golden Retriever with a malignant choroid melanoma treated with orbital exenteration had no recurrence or metastasis on thoracic radiographs, and was clinically healthy for 23 months after surgery (Miwa et al 2005). Another Golden Retriever (3 years old) with a choroidal melanoma, with retinal detachment and exophthalmos, was treated with eye enucleation. Histology was benign, but 21 months later gross systemic metastases (lung and liver) were diagnosed as histologically identical to the primary choroidal melanoma (Hyman et al 2002).

Melanoma in cats

In cats, anterior uveal melanomas are the most common primary intraocular tumour (**Figure 25.5**). Feline iris melanoma tends to present as a diffuse change rather than a discrete mass. A biopsy or aspirate may be helpful to differentiate benign iris melanosis, chronic uveitis and malignant melanoma in cats; however, obtaining a diagnostic sample may be difficult.

Malignant uveal melanoma in cats is very infiltrative and has a high rate of metastasis (Patnaik & Mooney 1988), frequently to liver and lungs. Iridial hyperpigmentation takes months to progress, and metastasis is late (1–3 years after eventual enucleation). Cats with melanomas that are larger and more invasive into the iris, ciliary body and scleral venous plexus (and with a higher mitotic index) are more likely to suffer metastasis. Benign anterior iridial melanoma may undergo late malignant transformation in a small number of cats to form larger, diffuse, malignant iris melanoma. In this subset of cats, early enucleation is important to avoid premature death from metastasis. Even with malignant transformation, cats with tumours confined histologically to the iris had good survival times, whereas cats with extensive ocular involvement or secondary glaucoma had shorter survival times (Kalishman et al 1998).

In humans with intraocular melanoma, the tissues around the eye are completely frozen to prevent flow of fluid and blood to or from the tumour, prior to enucleation. This is because manipulation of the tumour at enucleation increases intraocular pressure, significantly decreasing longevity by increasing metastatic potential. People are also advised not to rub or squeeze their eyelids (Fraunfelder et al 1977).

Figure 25.5 Uveal melanoma in a cat. (Courtesy R Straw.)

Primary ciliary body epithelial tumours

Examples of such tumours are adenocarcinoma and adenoma. They usually arise from the ciliary body or iris as a single mass extending from behind the iris into the pupil, and have been reported to infiltrate into the drainage angle and iris.

Carcinomas are the second most common primary intraocular tumour in dogs, rare in cats. They are locally invasive but usually have a low metastatic rate. Transillumination is used to diagnose the extent of the lesion and to differentiate benign ciliary body cysts (especially in the Golden Retriever) from ciliary body tumours.

Intraocular sarcoma

Canine

Histiocytic sarcoma (HS) may occur as an intraocular mass, especially in Rottweilers and Retrievers. In 15 of 26 dogs with ocular HS there were no concurrent systemic clinical signs at presentation, despite known systemic behaviour. Ocular HS has a poor prognosis, and may be differentiated from melanoma (usually a good prognosis) with immunohistochemistry (Naranjo et al 2007).

Feline

Sarcoma is the second most common intraocular tumour in cats, locally aggressive and highly metastatic. Previous ocular trauma which has occurred on an average of 5 years prior to sarcoma development is thought to be the cause (Dubielzig et al 1990). However, not all cases reported have a known previous history of trauma. Ocular trauma that triggers phthisis bulbi results in non-visual eyes that are at risk for late sarcoma development and should be enucleated (Ziess et al 2003). Feline leukaemia virus/feline sarcoma virus (FeLV/FeSV) does not seem to play a role in feline ocular sarcoma development (Cullen et al 1998). Enucleation prior to invasion of the optic nerve or sclera improves the prognosis (Dubielzig et al 1990). If complete removal is not possible due to tumour infiltration (even with orbital exenteration), recurrence is then expected and death will be from locally invasive tumour growth (into optic nerve, brain, periorbital tissues) within a few months of enucleation. The role of radiotherapy has not been evaluated in these patients. Metastasis is also reported.

Other primary tumours in dogs and cats are extremely rare. Blue-eyed dogs are at risk of developing spindle cell sarcoma in the anterior uvea.

Secondary/metastatic tumours

These are uncommon except for LSA (**Figure 25.6**). In one study, 37% of dogs with lymphoma presented with ocular involvement (second most common presenting sign after lymphadenopathy) (Krohne et al 1994). Survival times in dogs with intraocular LSA are 30–40% shorter than dogs without ocular involvement when treated with chemotherapy (Krohne et al 1994). Animals with multiple myeloma may present with ocular signs. Meningiomas can extend from the brain via the optic nerve.

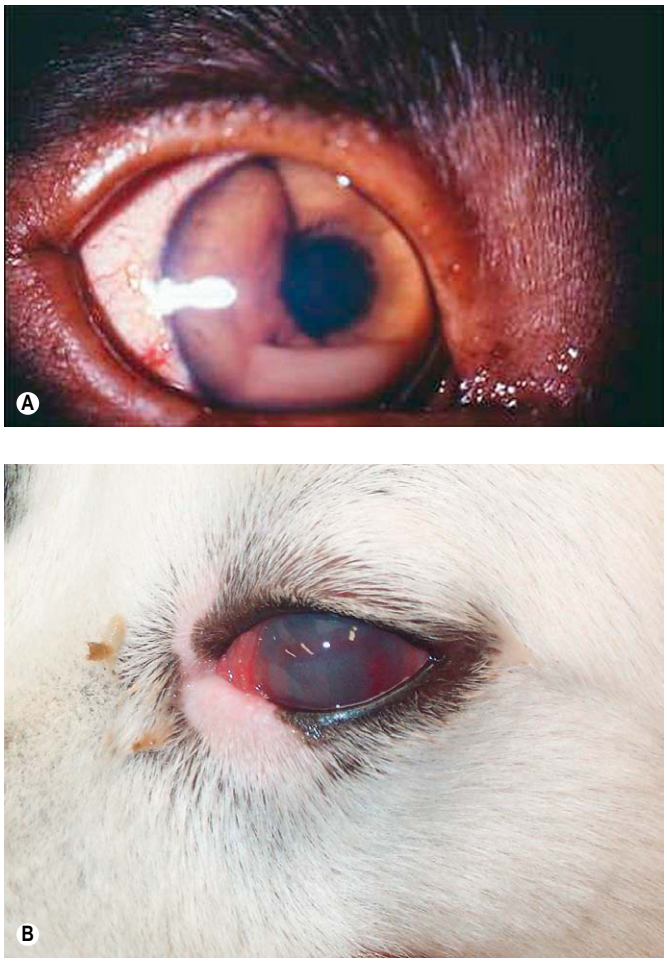

Figure 25.6 (**A**) Ocular lymphoma in a dog. (**B**) Lymphoma-induced uveitis in a dog.

Diagnostic work-up

Clinical appearance, history, signalment and staging are often suggestive of metastasis. It is important to look for another primary tumour (extraocular) which may have metastasized to the eye, or have ocular involvement (e.g. LSA, multiple myeloma). Other investigations include:

- ophthalmoscopy
- ultrasound of the eye and periorbital tissues
- transillumination, which can help differentiate cystic structures from more invasive masses.
- MRI/CT.

Often a definitive diagnosis is only obtained with enucleation and histopathology.

Treatment

In general, enucleation is advised if malignancy is suspected. However, for intraocular melanomas, there is only an overall 4% chance of metastasis, and enucleation has not been shown to prevent metastatic spread (Bussanich et al 1987). If intraocular malignant melanomas do metastasize, it is typically within 3 months of enucleation (Wilcock & Peiffer 1986).

Trans-scleral and transcorneal laser therapy may shrink some smaller intraocular tumours (Nasisse et al 1993). In

cats with iridial pigment changes which are progressive, or where there is pupil distortion, ciliary body or scleral invasion, or if uveitis is present, enucleation should be performed early.

For ciliary body epithelial tumours, treatment is removal of tumour and adjacent ciliary body (iridocyclectomy) and a reconstructive scleral graft or laser photoablation for small lesions, or enucleation for larger more infiltrative lesions. Small adenomas may remain asymptomatic and static for years, and may not need treatment.

Adenomas are benign and slow growing. Treat by removal of tumour and adjacent ciliary body (iridocyclectomy), and a reconstructive scleral graft or laser photoablation for small lesions, or enucleation for larger more infiltrative lesions. Small adenomas may remain asymptomatic and static for years, and may not need treatment. Adenomas may invade ciliary body or iris, but not the sclera, and may distort the pupil. Scleral invasion is consistent with adenocarcinoma.

The use of intraocular silicone prosthesis (ISP) implantation in the eyes of dogs and a cat with intraocular neoplasia has been reported (McLaughlin et al 1995). Two dogs had recurrence of local cancer 6 and 24 months after ISP, resulting in enucleation, and a cat had systemic metastasis 4 years after ISP. The ISP resulted in a dirty resection, allowing for tumour recurrence and metastasis. Primary ocular neoplasia confined to the globe is therefore better treated with early enucleation. In cases where there is systemic spread, there is questionable benefit to any surgery unless it is to provide pain relief.

Orbit (the cavity that encloses the eye) and retrobulbar tumours

Neoplasia is the most common cause of orbital disease in the dog. Orbital diseases in general are not as common in cats, and neoplasia is not as common as inflammatory disease in cats (Rühli & Spiess 1995). In both dogs and cats more than 90% of orbital tumours are malignant. In 44 dogs with confirmed orbital neoplasia, there were 18 tumour types, 95% of which were malignant. OSA, FSA and nasal adenocarcinoma were the most common tumour types (Hendrix & Gelatt 2000). In 23 dogs with confirmed orbital neoplasia, 91% of the tumours were malignant and 74% were primary neoplasms. Eleven tumour types of connective tissue, bone, epithelial and haemolymphatic origin were represented. Dogs most typically affected were purebred, female, and middle-aged (Kern 1985).

In dogs, most tumours are primaries, whereas in cats most are secondaries. In a study of 21 cats with orbital cancer, 14% were primary, 71% were secondary (from extension of local tumour into orbit) (**Figure 25.7**) and 14% were a manifestation of multicentric disease (Gilger et al 1992). Dogs with neoplastic disease were significantly older, had clinical signs for a longer time before initial examination, had more progressive onset of clinical signs, and more frequently had protrusion of the nictitating membrane, fever, and anorexia in one study of 29 dogs (Boroffka et al 2007). SCC was the most common cancer found in a study of 21 cats with orbital neoplasia; LSA, undifferentiated carcinoma, MM, adenocarcinoma, FSA, chondroma and HSA were others (Gilger et al 1992).

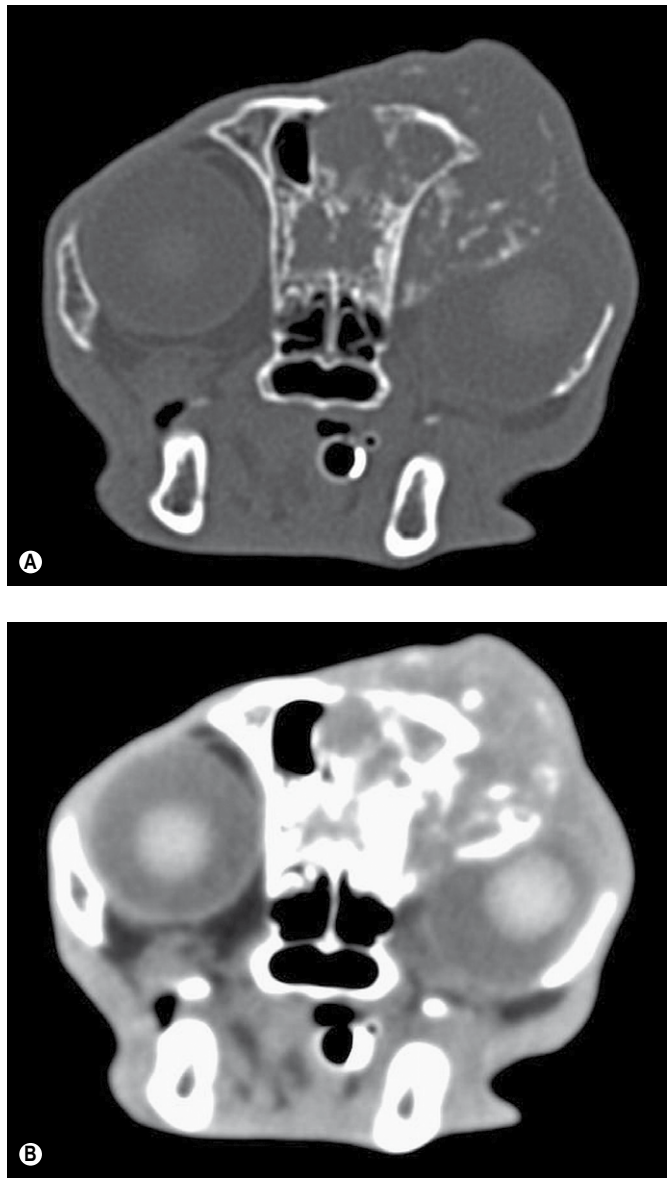

Figure 25.7 CT showing external compression of eye from a rapidly growing sarcoma: (**A**) pre-contrast; (**B**) post-contrast.

Primary, secondary, non-neoplastic and benign tumours of the orbit are outlined in Box 25.1. A primary retrobulbar teratoma causing exophthalmos has been reported in a cat (Wray et al 2007).

Clinical signs

Exophthalmos (reduced globe retropulsion) is the most common clinical sign. Exophthalmos may be accompanied by deviation of the globe, third eyelid prolapse, a widened palpebral fissure, conjunctival swelling/oedema/chemosis, epiphora, and a decreased ability to blink and subsequent exposure keratitis. Orbital neoplasia has been associated with enophthalmos in a cat (Pentlarge et al 1989). Of 25 cases of cats and dogs with retrobulbar tumours, 84% had exophthalmos, 40% had conjunctival hyperaemia, 20% had exposure keratitis and 20% had fundic abnormalities (Attali-Soussay et al 2001).

Box 25.1

Primary, secondary, non-neoplastic and benign tumours of the orbit

Primary tumours

- Osteosarcoma
- Multilobular osteochondrosarcoma
- Fibrosarcoma
- Chondrosarcoma
- Meningioma
- Malignant melanoma
- Mast cell tumour

Secondary tumours

- Squamous cell carcinoma of the oral cavity
- Nasal adenocarcinoma
- Cerebral meningioma
- Lymphoma

Non-neoplastic or benign tumours

- Retrobulbar abscess (e.g. foreign body, tooth root abscess, other penetrating wound)
- Orbital cellulitis
- Retrobulbar lipoma
- Zygomatic and lacrimal mucoceles
- Zygomatic and lacrimal adenomas (Giudice et al 2005, Headrick et al 2004)
- Haemorrhage/haematoma
- Cysts of the lacrimal duct (dacryops)
- Arteriovenous fistula
- Eosinophilic myositis

Physical examination

Check for abnormal globe position and decreased retropulsion. A general physical examination is required for a primary tumour outside the orbit, i.e.:

- palpate face for symmetry
- oral examination, e.g. maxillary mass, tooth root abscess
- nasal examination: discharge, epistaxis, sneezing; if present consider nasal work-up, e.g. rhinoscopy/CT/MRI, culture, biopsy, etc.
- otoscopic examination for tumours of the ear (Hayden 1976)
- skull palpation (e.g. masses, abscesses)
- palpate for enlarged regional lymph nodes.

A neurological examination is required to include cranial nerves.

Haematology may show a neutrophilia with neoplasia or infection. Anaemia may occur from chronic blood loss from nasal epistaxis or from a bleeding oral mass/infection.

Diagnostic work-up

- Three-dimensional imaging is very important (CT/MRI) (**Figure 25.8**).
- Retrobulbar FNA: ultrasound- or CT-guided if needed.
- Radiology (oral, nasal, cranial): this becomes redundant with CT/MRI.
- Periorbital ultrasound.

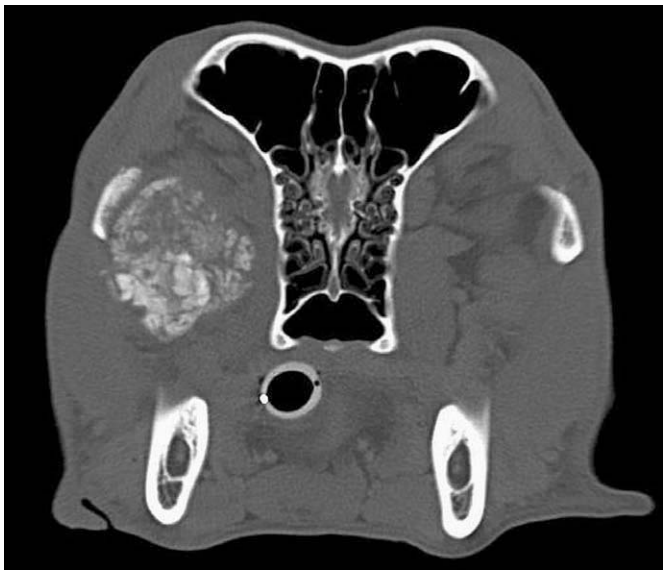

Figure 25.8 CT scan of a dog that presented for a possible retrobulbar mass.

- Ophthalmoscopy: indentation of posterior sclera, swelling of the optic nerve head (papilloedema), fundic abnormalities.
- Measurement of intraocular pressure may help differentiate ocular disease from retrobulbar disease.

Biopsy

Bakke & Kerty (2001) found that both CT and MRI were valuable to image the orbit. Contrast-enhanced, fat-suppressed MRI was better for imaging the optic nerve and any associated intracranial abnormality. CT was found the modality of choice for bony lesions.

Boroffka et al (2007) studied 29 dogs with unilateral neoplastic orbital disease and 16 dogs with unilateral non-neoplastic disease with CT or ultrasound imaging. Neoplastic masses were more clearly delineated on ultrasound or CT than were non-neoplastic masses. CT detected extraorbital involvement better than ultrasound. Neoplastic lesions were more frequently hypoechoic and homogeneous, and had globe indentation and bone involvement more frequently than did non-neoplastic lesions on ultrasound. Only neoplastic lesions were mineralized, and fluctuant fluid was more likely to be seen with non-neoplastic disease (Boroffka et al 2007).

MRI images are more useful than periorbital ultrasonography or radiography for orbital disease, and correctly discriminated between neoplasia, inflammatory disease and foreign body penetration in 88% of 25 small animal cases. Radiography was only found to be useful if there was significant bony disease extension/destruction beyond the orbit, where CT/MRI would be recommended (Dennis 2000).

Ultrasound detected an abnormality in 86% of dogs with retrobulbar disease. Ninety-one per cent of dogs with orbital bone lesions had retrobulbar cancer, which tended to be medial/ventral (because of extension from nasal sinuses) (Mason et al 2001).

In cats with orbital neoplasia, skull radiography was useful in 8 of 11 cats that had invasion of the orbit by adjacent neo-

plasms (Gilger et al 1992) but again the availability of CT/MRI is far superior for imaging these lesions.

Cytological examination was diagnostic for orbital neoplasia in 49% of the fine needle aspirates of the retrobulbar space, and 56% of non-surgical biopsies were diagnostic for orbital neoplasia (Hendrix & Gelatt 2000).

Examples of tools that may be used for further staging include:

- thoracic radiographs
- abdominal ultrasound
- nuclear scintigraphy/bone scans
- bone survey radiographs.

Treatment

Radiotherapy

Radiotherapy may be used as palliation for tumours with orbital extension, where the eye is preserved. Debulking of the tumour prior to radiotherapy may be feasible depending on the tumour type and invasiveness. Orbital exenteration could be followed by radiation for microscopic residual disease, with a curative intent. Complications of radiotherapy may include erythema to the skin and loss or change of colour of surrounding hair, keratoconjunctivitis sicca (KCS), keratopathy, uveitis and cataract formation.

Chemotherapy

Retrobulbar LSA or potentially MCT may be responsive to chemotherapy, but the treatment of choice would be radiation.

Surgery

Surgical techniques include orbitotomy and orbitectomy. Surgical resection, where possible, is the treatment of choice for primary orbital tumours. Orbitotomy is performed to preserve the globe, and is indicated for small, well-circumscribed tumours, retrieval of retrobulbar foreign bodies or drainage of retrobulbar abscesses.

Orbitectomy may be partial or complete, and involves removal of the globe, periorbital tissues and all or some of the orbit itself. Orbitectomy is not generally performed for secondary orbital neoplasia, but is generally done to remove all primary tumour with curative intent. According to Ramsey & Fox (1997):

> *Extensive surgical exposure of the orbit is limited to centimetres or fractions of a centimetre because of the compact anatomy and tight confines of the orbital region. Careful tissue manipulation, surgical dissection, and postoperative assessment are necessary to preserve the globe and functional vision when orbital disease endangers function.*

A simplified lateral orbitotomy has been described by Gilger et al (1994). This technique decreased surgical time, lessened tissue dissection and maintained exposure. The orbital ligament and temporalis aponeurosis from the dorsal zygomatic arch were cut to make a parallel zygomatic arch osteotomy. The zygomatic arch was then reflected ventrally to expose the orbit, and wired back into place at closure (Gilger et al 1994). A caudal auricular axial pattern flap can be used to close the wound created after orbital exenteration in the cat and dog (Stiles et al 2003) (**Figure 25.9**).

Figure 25.9 Caudal auricular axial pattern flap in a cat. (Courtesy R Straw.)

Prognosis

In a study by O'Brien et al (1996), total and partial orbitectomies were performed for invasive periorbital tumours in 24 dogs and 6 cats. The two most common tumours were multilobular osteochondrosarcoma (MLO) and SCC. Local recurrence occurred in 37%. The 1-year survival rate was 70% and disease-free interval was more than 1 year in greater than 50% of patients.

In 21 cats with orbital neoplasia, the mean survival time after diagnosis was 1.9 months. Ten cats were euthanized at the time of diagnosis because of extensive disease. Mean survival time of the other 11 cats was 4.3 months (Gilger et al 1992).

The globe could be safely preserved in most selected patients with maxillary sinus carcinoma invading the orbital floor, after preoperative radiation, without compromising survival or recurrence rates (Wu et al 1995).

Of 44 dogs with orbital neoplasia that died or were euthanized within 6 months of diagnosis, only 22% had undergone some form of therapy. In contrast, 86% of dogs surviving longer than 6 months post-diagnosis had undergone therapy, and 19% overall were still alive 1 year after diagnosis (Hendrix & Gelatt 2000).

Headrick et al (2004) have described canine lobular orbital adenoma in 15 dogs, with an average age of about 10 years; the adenomas were of salivary or lacrimal gland origin. Tissue was firm or friable, and histologically appeared as encapsulated lobules resembling well-differentiated lacrimal or salivary glands lacking ducts. Dogs presented with swollen/hyperaemic eyelids (4/15), third eyelid protrusion (3/15), conjunctival mass (6/15), exophthalmos (4/15), resistance to retropulsion (2/15) and strabismus (1/15). As recurrence was considered likely if excision was incomplete, orbital exenteration may be needed to prevent recurrence (Headrick et al 2004).

In 25 cases of orbital neoplasia in dogs and cats, surgical treatment by orbitotomy or exenteration was combined with chemotherapy and radiotherapy in some cases. The prognosis was poor with low survival times: 1 month in cats and 10 months in dogs, with a high rate of euthanasia (35%) at the time of diagnosis (Attali-Soussay et al 2001).

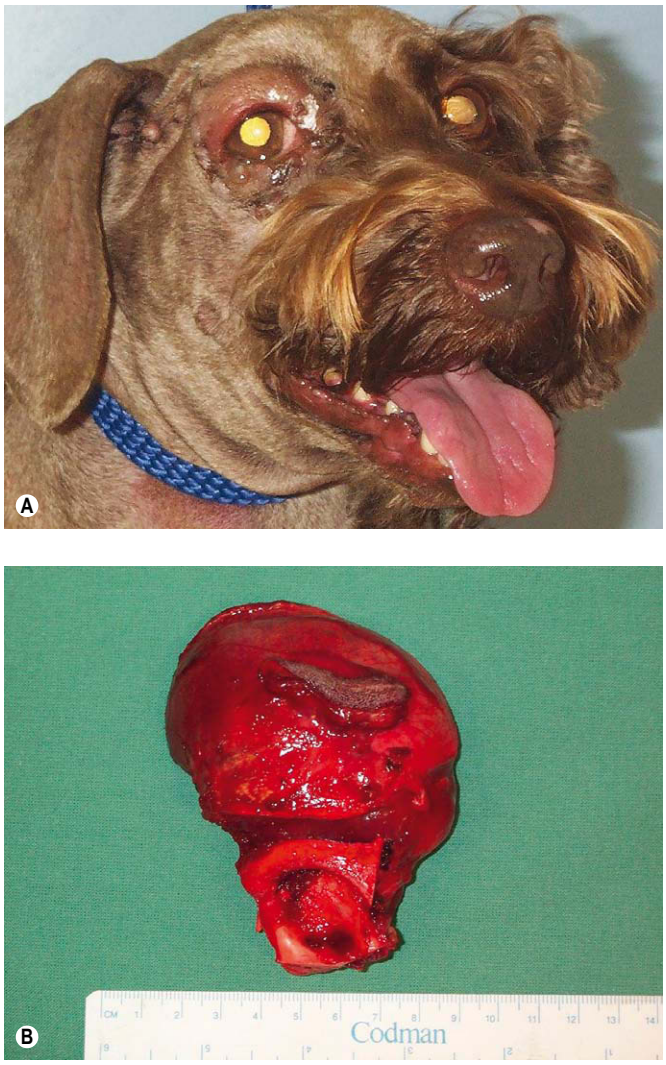

Figure 25.10 Infiltrating lipoma (**A**) preoperatively and (**B**) intraoperatively in a dog. (Courtesy R Straw.)

Occasional tumours located in the retrobulbar space include lipomas (**Figure 25.10**). Retrobulbar lipomas have an excellent prognosis with treatment. Preoperative FNA cytology and periorbital ultrasound may be useful for diagnosis (Williams & Haggett 2006).

A dog with progressive unilateral exophthalmos underwent removal of an orbital haemangiopericytoma by lateral orbitotomy, with no recurrence at 12-month follow-up (Beltran et al 2001).

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Tumours of the endocrine system

CANINE TUMOURS

Tumours of the thyroid

Thyroid tumours account for approximately 1–4% (Birchard & Roesel 1981, Loar 1986, Ogilvie 1996, Priester & McKay 1980, Waters & Scott-Moncrieff 1998, Wheeler 1989) of all canine tumours, and are typically seen in middle-aged to older dogs, with a median age of 9–10 years (Brodey & Kelly 1968, Harari et al 1986, Sullivan et al 1987). Breeds over-represented include the Boxer, Beagle and Golden Retriever (Harari et al 1986). Aetiology is unknown.

Most dogs with thyroid carcinoma are clinically euthyroid, and 55–60% have normal thyroid hormone concentrations (Feldman & Nelson 2004). Low serum thyroid hormone concentrations (hypothyroidism) are seen in 30–35% (Feldman & Nelson 2004) and may be due to destruction of the gland by the tumour, or possibly from pre-existing hypothyroidism, or from large thyroid tumours that produce significant amounts of inactive thyroid hormone which may suppress thyroid-stimulating hormone (TSH) secretion and lead to atrophy of the normal thyroid gland (Loar 1986). Only 10%–20% are functional (hyperthyroid) (Brodey & Kelly 1968, Feldman & Nelson 2004).

Thyroid adenomas are also seen (30–50% of thyroid tumours). They are usually small, non-functional and detected incidentally at post-mortem, but have been reported to reach >6 cm in size (Brodey & Kelly 1968, Leav et al 1976).

Thyroid carcinomas are classified as either follicular (solid or mixed) or parafollicular (medullary or C cell). Follicular thyroid carcinomas may be very large and invasive. These tumours are malignant, with metastasis found in 16–60% of patients at the time of initial diagnosis (Carver et al 1995, Harari et al 1986, Jeglum & Whereat 1983, Kent et al 2002, Withrow & McEwen 2001), and 60–80% of patients will ultimately develop metastatic disease at necropsy (Capen 1985, Leav et al 1976, Verschueren et al 1992). Metastasis is generally to regional lymph node and lungs (Brodey & Kelly 1968, Leav et al 1976). Other metastatic sites include adrenal gland, brain, heart, kidneys, liver and bone.

Thyroid carcinoma can also arise from ectopic tissue in the tongue, ventral neck and cranial mediastinum. Thirty-three per cent of thyroid carcinomas are freely mobile, without invasion into surrounding tissue; 67% are fixed, with dyspnoea, dysphonia, dysphagia and Horner's syndrome as clinical signs. Approximately one-third are bilateral (Feldman & Nelson 2004).

Clinical signs

In many cases thyroid tumours are not noticed by the client until they are extremely large and present to the veterinary surgeon for a mass on the ventral neck that is non-painful and not causing the dog any obvious discomfort. When questioned, the client may have noticed a change in phonation prior to presentation. Other clinical signs seen less frequently include dysphagia, dyspnoea and Horner's syndrome.

Diagnostic work-up

Fine needle aspiration (FNA) cytology can show malignant epithelial cells, with blood contamination common. A cervical mass with a bloody FNA is suspicious of thyroid carcinoma; the other differentials include neuroendocrine tumours or haemangiosarcoma. There is no need to perform an incisional biopsy preoperatively for a unilateral mobile neck mass if the FNA is highly suspicious of thyroid carcinoma, especially as this may greatly complicate surgical excision because the biopsy tract must be removed en bloc with the tumour. The purpose of an FNA is to differentiate a suspected thyroid mass from other causes of swelling in this area.

A definitive diagnosis requires a biopsy, which should be excisional if the tumour is surgically excisable (as judged by an experienced surgeon) or incisional if the tumour is fixed, bilateral or deemed not to be surgically excisable. The surgeon is warned that these tumours are extremely vascular (particularly when fixed and invasive) and biopsy or excision may cause significant haemorrhage. Even a small surgical procedure can result in considerable blood loss due to the highly vascular nature of these tumours.

An ultrasound of the neck may be beneficial for diagnosis (e.g. identification of a mass of thyroid origin, ultrasound-guided FNA, assessing tumour vascularity) and may also be used to examine the regional (e.g. cervical and retropharyngeal) lymph nodes for metastasis (Wisner & Nyland 1998, Wisner et al 1994). However, a CT or MRI scan is of much greater value in these cases.

Evaluation of T4 may be useful to check thyroid status but is rarely of clinical significance. Scintigraphy, when available, may be useful as an abnormal accumulation of sodium pertechnetate ($Tc99^{m}$) may also assist in the diagnosis of ectopic thyroid malignancy. The functional capability of normal thyroid should be determined as part of the diagnostic work-up and as part of follow-up evaluation (Marks et al 1994). Iodine-131 (^{131}I) uptake may also be useful for diagnosis of local tumour.

Staging

Regional lymph nodes should be palpated for enlargement and aspirated if suspicious. Haematology, serum biochemistry and urinalysis are routinely performed as part of a general health assessment. Survey thoracic radiographs are standard. A thoracic CT is more sensitive than thoracic radiographs to rule out disseminated disease. Cervical ultrasound can be useful, but for planning treatment of large fixed tumours a contrast-enhanced CT or MRI is required. Nuclear scintigraphy can be used for determining function and identifying ectopic malignant tissue. Scintigraphy is also useful for staging.

Differential diagnoses include abscess, granuloma, salivary mucocele, salivary adenocarcinoma, lymphoma, carotid body tumours (**Figure 26.1**), haemangiosarcoma or other sarcoma, and finally metastasis from oral squamous cell carcinoma (SCC).

Treatment

Options depend on the size, degree of invasion, clinical signs of hyperthyroidism and the availability of radiotherapy and nuclear medicine.

Surgery

This is the treatment of choice for freely movable masses. It is important that an experienced oncological surgeon evaluates 'movability' as surgically excisable masses can seem fixed to the inexperienced surgeon. The surrounding trachea and neck muscles and deeper location of the neck mass can 'hold' the tumour in place and give a false idea of fixation (**Figure 26.2**). In the authors' experience, if it is a rounded, well-circumscribed mass and is even slightly movable, it is likely to be surgically excisable. If it is large, invasive and totally fixed and immobile, it is not surgically excisable, and attempting to remove it would likely result in a great deal of haemorrhage. Some are very obviously freely mobile and these are most amenable to surgical excision.

Unilaterally, the carotid artery, jugular vein and vagosympathetic trunk can be sacrificed with minimal morbidity. Surgery can be complicated by local invasion and excessive haemorrhage or regional coagulopathy.

Prognosis with surgery

- *Freely mobile*: the prognosis is good with a median survival time (MST) of 36 months, a 1-year survival rate

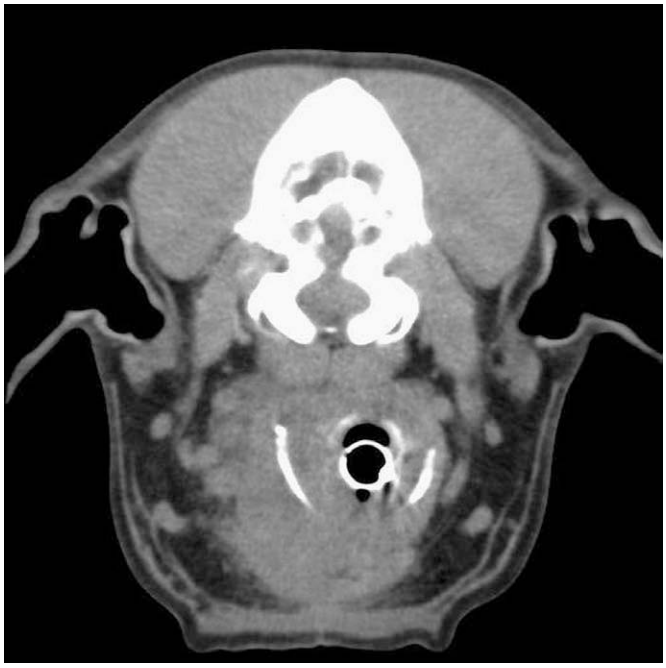

Figure 26.1 CT scan of neuroendocrine tumour (major differential for thyroid carcinoma).

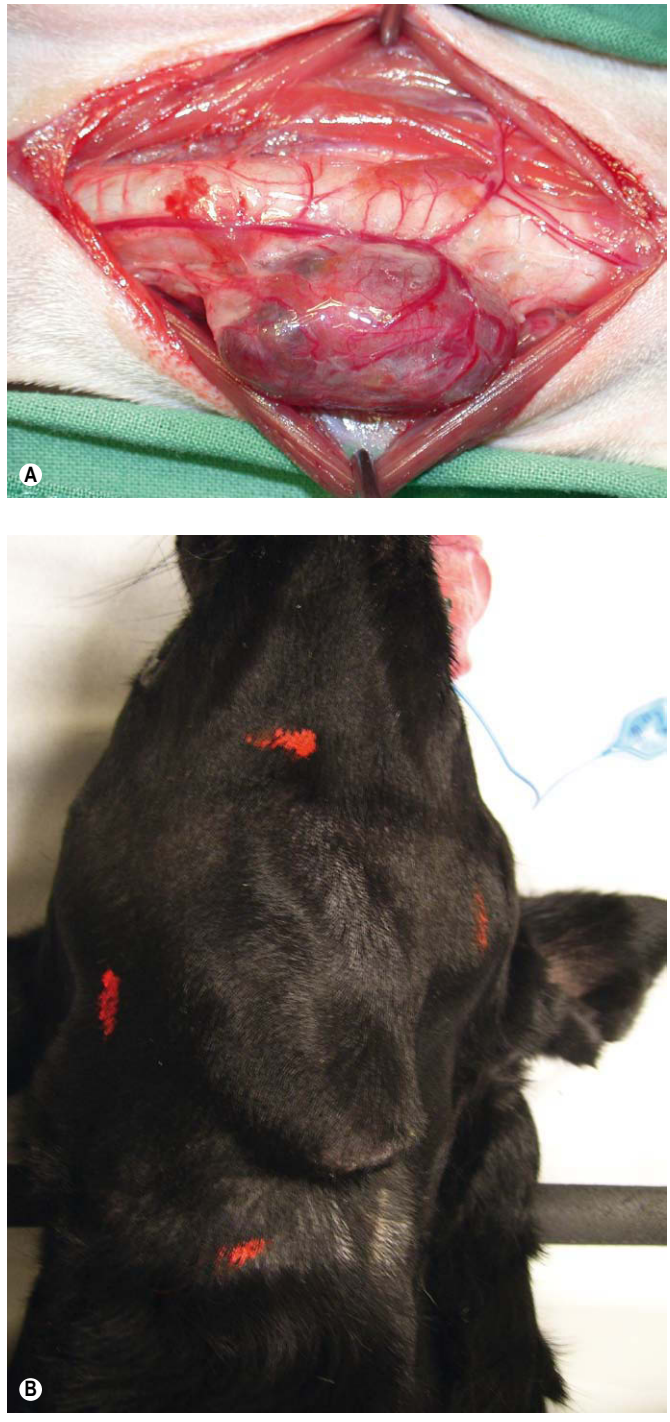

Figure 26.2 (**A**) Thyroid tumour at time of surgery. (**B**) Large thyroid carcinoma before radiotherapy; this tumour ultimately was excised after a good response to radiation.

of 75% and a 2-year survival rate of 70% (Klein et al 1995).

- *Fixed*: with surgery alone the prognosis is poor with an MST of 10 months, a 1-year survival rate of 5% and a 2-year survival rate of 10% (Carver et al 1995).

Radiotherapy

Radiation has a number of applications in the management of thyroid carcinomas. It can be used as adjunctive therapy to reduce recurrence after incomplete resection or to shrink tumours down prior to surgery. In the latter instance it is the deep margin that is important to evaluate for making a non-surgical patient into a surgical one (see **Figure 26.2B**).

Radiotherapy is the treatment of choice for large non-resectable tumours. A number of different protocols have been used. Théon et al (2000) reported a progression-free interval of 80% at 1 year and 72% at 3 years using a hyperfractionated protocol. The metastatic rate was 28% and the MST was 24.5 months.

For dogs with non-resectable disease, a hypofractionated protocol (4 once-weekly fractions of 900 cGy) resulted in good long-term control with an MST of 24 months. A complete response was seen in 11% of patients, with most dogs typically having a partial response (89%). No difference in survival was noted between dogs with and without metastatic disease at the time of diagnosis, suggesting that metastatic lesions are very slow growing (Brearley et al 1999).

Chemotherapy

Overall the value of chemotherapy in the management of thyroid carcinomas is debatable. In one study a partial response was seen in 30–50% of dogs treated with either doxorubicin or cisplatin. Cisplatin 9% (1/11) had a complete response and 54% (6/11) a partial response. The overall MST was 98 days although the MST for responders was 322 days (Fineman et al 1998).

Iodine-131 (^{131}I)

Responses to ^{131}I have been reported but the number of cases is small. ^{131}I is indicated for non-resectable thyroid carcinoma, incomplete resection of thyroid carcinoma and metastatic thyroid carcinoma (Worth et al 2005), but is rarely applicable in most cases because of radiation protection issues and the availability of resources. In a recent study of ^{131}I therapy (± surgery) in 39 dogs with non-resectable thyroid tumours, prolonged survival times were achieved, regardless of serum thyroxine concentration prior to treatment, although three dogs died of bone marrow suppression. Dogs with local or regional tumours lived a median of 839 days; dogs with metastasis lived a median of 366 days (Turrel et al 2006). In another study, 11 dogs that received ^{131}I adjunctively to surgery had an MST of 34 months, dogs receiving ^{131}I alone had an MST of 30 months and dogs with no treatment had an MST of only 3 months (Worth et al 2005).

Prognosis

An early diagnosis, with a freely movable, small primary tumour, treated with complete surgical excision, correlates to a good to excellent prognosis. A delayed diagnosis allows further growth, invasion and fixation of the primary tumour, and a poorer overall prognosis.

Large tumours tend to be poorer candidates for surgery, and are more likely to have metastasized. Tumours >20 cm^3 or >5 cm in diameter are at a higher risk of developing metastatic disease (Leav et al 1976).

If the tumour is non-resectable, the options for treatment are then considered to be palliative, i.e. radiotherapy (treatment of choice), chemotherapy or ^{131}I.

Patients with bilateral thyroid carcinoma have a 16 times greater risk of developing metastatic disease (Théon et al 2000). In addition, patients with non-medullary thyroid carcinomas may be more likely to develop metastatic disease (Carver et al 1995).

Tumours of the parathyroid gland

Tumours of the parathyroid gland are uncommon and typically are benign (adenomas/hyperplasia). Carcinomas are seen less frequently (Berger & Feldman 1987). Typically older dogs are affected (age range 7–13 years) with no apparent sex predilection. Keeshonds may be over-represented (Goldstein et al 2007, Skelly & Franklin 2007, Weir et al 1986).

Clinical signs

These patients typically present with polyuria/polydipsia (PU/PD). Other non-specific signs include listlessness and muscle weakness (Berger & Feldman 1987). Calcium-based urinary calculi may also occur (DeVries et al 1993).

Diagnostic work-up

Any patient presenting for PU/PD should have a full biochemistry profile carried out, including total and ionized calcium. Serum calcium is either ionized (free, i.e. biologically active: 56%), chelated (bound to phosphate, bicarbonate, sulphate, citrate or lactate: 10%) or protein-bound (34%) (Schenck et al 1995). The identification of hypercalcaemia as the cause of PU/PD means an investigation into the underlying causes for hypercalcaemia.

Differential diagnoses include primary hyperparathyroidism, a number of neoplastic disorders including lymphoma, multiple myeloma and anal sac adenocarcinoma, and metabolic disorders including hypoadrenocorticism, vitamin D toxicity, renal failure and skeletal disorders. Laboratory error (lipaemia, haemoconcentration, haemolysis) can also cause hypercalcaemia. Elevations in serum albumin or globulins may elevate total serum calcium, but the free/ionized/biologically active calcium remains unchanged/normal.

As parathyroid gland tumours are rare, typically other causes of hypercalcaemia are ruled out first. Thorough physical examination, including a rectal examination, is essential. Thoracic and abdominal radiographs and abdominal ultrasound rule out other causes of hypercalcaemia. Other tests would include haematology, ACTH stimulation test and bone marrow evaluation. If no other cause of hypercalcaemia is identified, measurement of serum parathormone (PTH) and parathormone-related peptide (PTH-rP) is indicated. However, the improved availability of specific hormonal tests means that, in patients with a high index of suspicion for parathyroid gland tumours, PTH and PTH-rP should be assessed early in the diagnostic process.

Primary hyperparathyroidism occurs with elevated total serum calcium, normal to increased serum PTH, and increased ionized calcium.

The diagnosis of primary hyperparathyroidism is based on ruling out other causes of hypercalcaemia, and finding an elevated serum PTH relative to serum calcium concentration. Serum PTH should decrease as serum calcium increases in normal dogs. Hyperparathyroid dogs can still have a PTH within the normal reference range, but PTH should be reduced in a normal dog with elevated serum calcium.

Ultrasound of the thyroid and parathyroid glands can assist in diagnosis and aid the surgeon not only to localize the tumour but also to check for multiple tumours, as multiple parathyroid adenomas are not uncommon in dogs (DeVries et al 1993, Feldman & Nelson 2004). Eighty per cent of dogs have single gland involvement and 20% have multiple gland involvement (Arnaud & Kolb 1991). Although ultrasound findings correlate well with surgical findings (Gear et al 2005), in many cases cervical ultrasound may be negative. Exploratory surgery is indicated if primary hyperparathyroidism is suspected based on PTH and ionized calcium levels regardless of negative cervical ultrasound findings. Scintigraphy can also assist in diagnosis (Matwichuk et al 1996).

Treatment

Preoperatively, hypercalcaemia can be managed with saline diuresis, but only until the patient is stable enough for surgery. The treatment of choice is prompt surgical excision of the affected parathyroid gland(s). Surgical exploration should be performed via a ventral midline approach, to allow for exploration and examination of each thyroid gland and the associated four parathyroid glands (**Figure 26.3**). All four parathyroid glands can be removed, although lifelong calcium and vitamin D supplementation will be required.

Enlargement of all four glands due to primary hyperparathyroidism is reported (DeVries et al 1993, Feldman & Nelson 2004); however, it is extremely rare and generally suggests a diagnosis other than hyperparathyroidism (i.e. secondary hyperplasia). As long as one of the parathyroid glands is not removed there is no risk of permanent hypocalcaemia.

Postoperative hypocalcaemia is a common short-term complication (usually within 1–4 days) after removal of a parathyroid tumour because of tumour-induced atrophy of the remaining glands, and management of serum calcium is critical until the remaining glands are functioning normally. Providing there has been no permanent damage to the kidneys from prolonged hypercalcaemia, the overall prognosis after surgery is good.

Treatment of parathyroid tumours using ultrasound-guided intralesional ethanol injections and radiofrequency heat ablation has been described (Long et al 1999, Pollard et al 2001). Intralesional ethanol injections appear the more successful of the two techniques.

Prognosis

In the rare cases of parathyroid carcinoma the prognosis is still good. Feldman & Nelson (2004) report that 5–10% of their canine cases of primary hyperparathyroidism were given a diagnosis of a parathyroid carcinoma on histology, but none had distant metastasis. This has also been the clinical experience of the authors, although one patient died of metastatic disease within 6 months. Non-malignant parathyroid tissue can have many of the histological features of malignancy and the surgeon is therefore justified in giving a cautiously optimistic prognosis for cases of parathyroid carcinoma that appear to have all the clinical features of parathyroid hyperplasia or adenoma. The role of radiotherapy or chemotherapy in patients with parathyroid carcinoma has not been explored, and would seem hard to justify given the previous comments.

For patients with persistent hypercalcaemia due to metastatic spread, medical management may provide some symptomatic relief. Diuresis with 0.9% NaCl should be instigated and when fully hydrated calcium-wasting diuretics (furosemide) may be used. It is important to ensure full hydration before using diuretics to prevent any further renal damage. Prednisolone is rarely beneficial but other agents, including calcitonin and bisphosphonates, may provide some symptomatic relief. The prognosis for the patient with metastatic spread is poor.

APUDomas

APUD stands for amine precursor uptake and decarboxylation. These tumours are of neuroendocrine origin and arise from specialized cells located in the pancreas, gastrointestinal tract, pituitary, thyroid and adrenal glands. APUD cells possess a neuron-specific enolase and the presence of this enolase can be used to identify these tumours histologically. Most APUDomas are of pancreatic origin and include insulinoma, glucagonoma and gastrinoma.

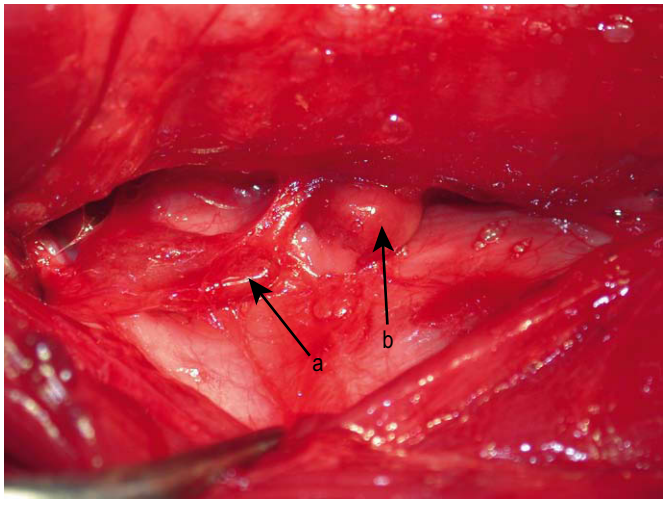

Figure 26.3 **a**) Parathyroid adenoma and **b**) small thyroid carcinoma.

Pancreas

Insulinoma

Insulinoma is the most common tumour of the canine pancreas. It is extremely rare in the cat. The cell of origin is the pancreatic beta cells and the majority of insulinomas (80%) are functional carcinomas. Visceral metastases to the regional lymph nodes and liver are common.

Signalment

Insulinoma is seen in middle-aged to older dogs, with an increased incidence in German Shepherds, Irish Setters and Golden Retrievers (Caywood et al 1998). However, any breed of dog may be affected.

Clinical signs

These include weakness, lethargy, ataxia, seizures, muscle tremors, collapse, and ultimately coma. These are often episodic and are a consequence of hypoglycaemia that results in neuroglycopenia and increased catecholamine production. Peripheral neuropathies have also been reported (Braund et al 1987, Shahar et al 1985, Van Ham et al 1997).

Diagnostic work-up

Insulinoma should be suspected when there is a high serum insulin level and associated hypoglycaemia.

Ultrasound

Ultrasonography may be helpful, but many of these tumours are small and difficult to detect on ultrasound. In one study, ultrasound identified 75% of pancreatic neoplasias but was only 55% sensitive for detecting metastasis (Lamb et al 1995).

CT and scintigraphy

CT identified 10 of 14 pancreatic masses but overestimated metastasis (Robben et al 2005).

Scintigraphy and single photon emission CT with radiolabelled octreotide (somatostatin analogue) appear as good as ultrasound for detecting primary pancreatic neoplasia, but have poor sensitivity for detecting metastasis (Robben et al 2005). Robben et al (1997) reported visualization and localization of primary pancreatic tumour and/or metastasis in five of six dogs; multiple metastases (<3 mm) were found in the liver at necropsy in the remaining dog, apparently too small to be visualized by single photon emission CT. Radiolabelled pentetreotide (somatostatin analogue) scintigraphy accurately predicted the anatomical location of the primary tumour in one of four dogs (Garden et al 2005).

Although imaging modalities can be helpful for diagnosis and staging, a definitive diagnosis and accurate staging for prognosis require exploratory surgery and biopsy.

Surgery

The treatment of choice is partial pancreatectomy to remove the primary and, if possible, any metastatic lesions. Insulinomas are malignant, with most patients having microscopic or gross metastases at the time of surgery. In one study, 14 dogs with suspected gross metastases at surgery had this confirmed by biopsy in only 8 (Tobin et al 1999). The most common site of metastases is to the regional lymph nodes and liver.

In 92% of cases, an obvious mass was found in the pancreas at the time of surgery (Feldman & Nelson 2004). The primary tumour may be in either lobe (equal frequency) and up to 15% have multiple nodules (Caywood et al 1998, Tobin et al 1999). Feldman & Nelson (2004) reported 42% were in the right (duodenal) lobe, 41% in the left (splenic) lobe and 17% in the central region (body). Most tumours are visible but some are not, and are only found with gentle palpation of the pancreas. The surgeon should handle the pancreas very gently and carefully, as finding the tumour can be difficult once the pancreas has been traumatized and inflamed with repeated palpations. Minimal margins (1–2 mm) of grossly normal pancreas around the mass appear adequate, and there are no data to say whether or not taking a wider margin of grossly normal pancreas is helpful for survival or recurrence. Haemoclips, suture–fracture technique or TA-30 staples can be used to assist removal.

Intraoperative ultrasound has been used to identify small tumours (Robben et al 2005). If no tumour can be found in the pancreas, one option is to remove half of the pancreas and send it for histopathology, in the hope that tumour will be identified. If no discrete tumour is found, the pathologist should check for diffuse microscopic islet cell carcinoma (reported in 4 of 85 dogs). If the resected pancreas fails to show any abnormal tissue, the other half could then be removed, as only a small amount of pancreatic tissue is needed to maintain endocrine and exocrine pancreatic function in the normal animal. Feldman & Nelson (2004) recommend against removal of insulinomas from the body (central) part of the pancreas for fear of causing severe, life-threatening pancreatitis, but this has not been the authors' experience. The blood supply to the pancreas is important and should be reviewed prior to surgery.

The regional lymph nodes should be removed if visible or palpable. Removal of suspected metastases from the liver can be difficult if they appear as multiple small nodules, but a liver biopsy should always be taken for staging purposes. The surgeon should endeavour to remove as much neoplastic tissue as possible, because even if not all the cancer is resectable, debulking can alleviate clinical signs for some months. Survival can be prolonged in dogs that undergo tumour debulking and medical management, compared to dogs treated medically only (Polton et al 2007, Tobin et al 1999).

With surgery alone the MST was 381 days with survival time being unrelated to the location of the tumour within the pancreas (Tobin et al 1999). Caywood et al (1998) reported the following prognosis with surgery: tumours confined to pancreas (stage I) were normoglycaemic for a median of 14 months postoperatively, dogs with metastasis to regional lymph nodes (stage II) or distant metastasis (stage III) were normoglycaemic for a median of about 1 month. Dogs with stage I or II disease had an MST of 18 months, dogs with stage III disease had an MST of <6 months. Dogs treated with partial pancreatectomy will eventually re-present with clinical signs of hypoglycaemia due to metastases. It is advised in these dogs to start medical management at the time because this will greatly increase survival times (Polton et al 2007).

A repeat surgery to debulk tumour and metastases after a relapse of hypoglycaemia may also prolong survival further, especially if in combination with ongoing medical management. Abdominal ultrasound is generally performed to try to assess the feasibility of such a surgery.

Blood glucose levels and surgery

Preoperative, intraoperative (every 30 minutes of surgery time) and postoperative measurements of blood glucose are required, with intravenous supplementation with 2.5–5% dextrose-containing fluids until glucose levels remain stable. A constant rate infusion (CRI) of glucose and dexamethasone can also be used to help prevent severe hypoglycaemia if 5% dextrose supplementation is inadequate. In the authors'

experience, the blood glucose generally starts to climb within a few hours of surgical removal of the insulinoma. Dextrose solutions of 7.5–10% can be utilized, if necessary, through a central (jugular) catheter.

Medical management

For the patient presenting with hypoglycaemic seizures, 1–5 ml 50% dextrose is given slowly intravenously, and the patient is fed as soon as able to eat.

For patients with inoperable insulinomas, or those with evidence of metastases or recurrent clinical signs after successful surgery, medical management can prolong good quality of life for many months. In these patients the goal of medical treatment is to prevent the clinical signs associated with hypoglycaemia. These patients will already have adapted to some degree of hypoglycaemia and, therefore, you do not have to achieve normal levels with treatment but only a level at which the patient is comfortable. However, medical management is no substitute for surgery in the majority of patients. MST for patients on prednisolone only was 74 days in one study (Tobin et al 1999).

Many patients can be kept relatively stable by frequent feeding of diets rich in protein and complex carbohydrates, sometimes up to six meals daily. However, ultimately drug therapy is required.

The first-line drug should be prednisolone. Prednisolone inhibits the action of insulin on peripheral tissue and stimulates glycogenolysis. Initial dose is 1 mg/kg, then reduced to the lowest effective dose.

The second-line drug is diazoxide, which inhibits secretion of insulin by beta cells by blocking calcium mobilization, stimulates gluconeogenesis and glycogenolysis, and inhibits tissue use of glucose, therefore decreasing glucose utilization. Typical dose is 3.3 mg/kg every 8 hours, which can be increased up to 20 mg/kg every 8 hours. Diazoxide should be used in conjunction with prednisolone to maintain blood glucose high enough to prevent signs of neuroglycopenia.

Other agents include:

- *Streptozotocin* (nitrosourea): selectively toxic to beta cells, it is nephrotoxic to dogs, but safe if administered with aggressive saline diuresis. It can cause diabetes mellitus. There is minimal advantage in using this drug, because dogs treated with surgery alone have similar median disease-free intervals. Streptozotocin may provide a rapid resolution of paraneoplastic peripheral neuropathy (Moore et al 2002).
- *Sandostatin* (somatostatin analogue): has a wide range of effects and is very effective in humans with insulinomas. In one small study in dogs, four out of five had some response (Lothrop 1989), but it is very expensive.

Glucagonoma

These are rare tumours arising from the alpha cells of the pancreatic islets. The clinical signs are associated with the catabolic effects of glucagon. Diabetes mellitus and superficial necrolytic dermatitis are associated with this tumour (Gross & O'Brien 1989), although not all dogs with this condition have a glucagonoma (Turnwald et al 1989). In patients with clinical signs compatible with glucagonoma serum glucagon levels should be checked.

The treatment of choice for patients with glucagonoma is surgical resection. The number of reported cases is low and all dogs had metastatic disease at the time of diagnosis, making the prognosis poor. CT successfully identified a glucagonoma in one dog; ultrasonography was not found to be helpful. Liver function tests were normal in dogs with glucagonoma, but abnormal in dogs with superficial necrolytic dermatitis secondary to liver disease (Ward & Washabau 2005).

Gastrinoma

These tumours arise from non-beta islet cells of the pancreas. The actual cell of origin is unknown because the adult pancreas does not produce gastrin. The D cells produce gastrin in foetal life but in the adult they secrete somatostatin. Gastrinomas may be associated with multiple endocrine neoplasia (MEN) syndrome.

Clinical signs

Clinical signs include chronic vomiting, anorexia, weight loss, gastroduodenal ulceration and chronic small bowel diarrhoea. It is a rare tumour in dogs but should be considered in any patient with gastroduodenal ulcers that respond well to H_2-receptor antagonist therapy but relapse when treatment ceases.

Diagnostic work-up

In patients where a gastrinoma is suspected, a fasting serum gastrin level should be assessed, although levels may be normal in the early stages. Normal = <100 pg/ml in dogs and cats. In dogs with gastrinomas levels are typically in the order of more than three times the upper limit of the normal reference value (Feldman & Nelson 2004). Most (80%) dogs and cats with gastrinoma have gastrointestinal ulceration (Zerbe & Washabau 2000), and endoscopy and ultrasound can demonstrate this. Abdominal ultrasound will not reliably show a pancreatic tumour as they are usually small or microscopic (Roche et al 1982). Scintigraphy with radiolabelled somatostatin analogues often assists in diagnosis (Gibril et al 1996, Schirmer et al 1995) and can also identify which gastrinomas may benefit from octreotide (a long-acting somatostatin analogue which decreases gastrin release) (Ellison et al 1986).

However, surgery is a better way to investigate further if a gastrinoma is suspected based on clinical signs and an elevated fasting serum gastrin level. Surgery allows a definitive diagnosis via pancreatic biopsy, removal of ulcers, and removal of regional lymph node or liver metastases, if possible. Gastrinomas have a predilection for the right lobe and body of the pancreas (Zerbe & Washabau 2000), so removal of the right pancreatic lobe should be performed if no discrete tumour can be found.

Treatment

A combination of drugs have been used, including H_2-receptor antagonists such as ranitidine, cimetidine and famotidine; proton pump inhibitors such as omeprazole; diffusion barriers such as sucralfate; synthetic prostaglandins, e.g. misoprostol, and somatostatin analogues, e.g. octreotide.

Prognosis

Gastrinomas are aggressive with metastasis common (regional lymph nodes, liver, spleen and/or mesentery) in 70% of dogs

at diagnosis (Altschul et al 1997, Feldman & Nelson 2004, Green & Gartrell 1997). Surgical debulking of tumour reduces gastrin secretion and enhances adjunctive medical management (Zerbe & Washabau 2000). An improved prognosis seems likely with early diagnosis, treatment with surgery and adjunctive medical management. Dogs and cats treated surgically and/or medically survive from 1 week to 2 years, most dying <8 months after diagnosis (Zerbe 1992). Altschul et al (1997) reported that surgery and combination therapy with an H_2 blocker, omeprazole, sucralfate and octreotide allowed one canine patient to survive for 14 months. Omeprazole and surgical biopsy resulted in a 2-year survival for another dog (Brooks & Watson 1997). A 26-month disease-free interval with medical management alone (sucralfate, omeprazole and ranitidine) has also been reported (Hughes 2006).

Adrenal gland

Hyperadrenocorticism due to an adrenocortical tumour accounts for ~15% of naturally occurring hyperadrenocorticism in dogs (Feldman & Nelson 2004, Reusch & Feldman 1991). The ratio of adenoma to carcinoma is approximately 1:1 (Feldman & Nelson 2004, Scavelli et al 1986). However, not all adrenal tumours are secretory and may be found during the diagnostic work-up for other problems.

To differentiate a primary adrenal tumour from pituitary-dependent hyperadrenocorticism (PDH) a number of diagnostic tests are required. Rarely dogs may have concurrent PDH and adrenal tumours (Greco et al 1999), which can cause confusion when trying to understand test results.

Diagnostic work-up

Blood tests

- *Low-dose dexamethasone test*: this is the most sensitive screening test for hyperadrenocorticism but does not differentiate the different forms of the disease.
- *High-dose dexamethasone test*: dogs with adrenocortical tumours do not suppress, but up to 30% of patients with pituitary hyperadrenocorticism will also not suppress.
- *Endogenous ACTH*: endogenous ACTH concentration, when undetectable, is consistent with an adrenal tumour or iatrogenic hyperadrenocorticism and must now be considered the screening test of choice for hyperadrenocorticism of adrenal gland origin.

Abdominal radiography

Calcification of the adrenal gland in a dog with hyperadrenocorticism does not suggest neoplasia, as about 50% of both adenomas and carcinomas calcify (Penninck et al 1988, Reusch & Feldman 1991).

Positive contrast caudal vena caval angiography can show extension of tumour into the vena cava by highlighting a filling defect in the vein.

Abdominal ultrasonography

In conjunction with blood tests, this is an accurate diagnostic test, although imaging right adrenal gland tumours in large overweight dogs can be very challenging. For these cases, contrast-enhanced CT or MRI is recommended. Enlargement of one adrenal gland and atrophy of the contralateral gland is suggestive of an adrenal tumour. However, bilateral tumours have been identified in some dogs (Ford et al 1993, Hoerauf & Reusch 1999).

For carcinomas, extension into the vena cava may be imaged and/or the presence of metastases to regional lymph nodes and liver may be identified.

Kyles et al (2003) reported abdominal ultrasound was 80% sensitive and 90% specific for the detection of caval thrombi in dogs with adrenal gland tumours.

CT/MRI scan

In cases where abdominal ultrasound is unable to adequately image the adrenal glands, and local invasion into the surrounding structures (particularly the vena cava) is suspected, a contrast-enhanced CT or MRI scan is advisable to assist in surgical planning.

Staging

The thorax and abdomen should be imaged to screen for metastasis prior to any surgery. Thoracic radiographs and abdominal ultrasound are traditional methods; contrast-enhanced thoracic and abdominal CT or MRI may be more sensitive.

Treatment

Surgery

Adrenalectomy is the treatment of choice and in the case of adenomas carries a good prognosis (**Figure 26.4**). Even for patients with adrenal carcinomas, if surgery is possible it is the best treatment option. The overall prognosis for dogs treated surgically is excellent, as long as they survive the first 1–4 weeks after surgery. An average survival time after surgery is 36 months.

For patients with large or extensively invasive tumours adrenalectomy may not be an option due to the high morbidity associated with surgery; however, only 9 of 144 unilateral adrenal tumours were deemed inoperable at surgery (0.06%) (Feldman & Nelson 2004). Kyles et al (2003) showed that the presence of a caval tumour thrombus did not adversely affect prognosis, as long as an experienced surgeon performed adrenalectomy and thrombectomy. The autogenous jugular vein has also been used in reconstructive vascular surgeries involving the cava (White et al 1996) and caval grafts using polytetrafluoroethylene have also been reported (Lascelles et al 2003).

The surgeon and client need to be aware of the high rate of postsurgical complications that can arise, including pneumonia, pancreatitis, pulmonary thromboembolism, acute renal failure and hypoadrenocorticism. The mortality rate with surgery is approximately 20% (Anderson et al 2001, Kyles et al 2003, Van Sluijs et al 1995). As none of these studies reported a specific medical management protocol prior to surgery, it is not known if medical management reduces the risk of complications.

Human patients with Cushing's syndrome have a four-fold increase in the incidence of pulmonary embolism and deep vein thrombosis, and a four-fold mortality rate compared with the general population (Jacoby et al 2001). To try to reduce the risk of a fatal thromboembolism, the authors advise medical management for a few weeks before surgery if possible. Although this is not proven to be beneficial, for the

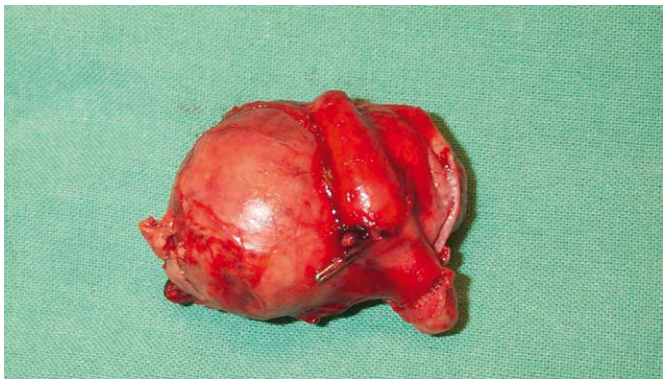

Figure 26.4 Adrenal tumour. (Courtesy R Straw.)

surgeon and client it seems reasonable to 'cover all bases'. It is tragic to lose a patient to a pulmonary thromboembolism after proficient surgical resection of the adrenal mass. Our current regime is trilostane for 2 weeks preoperatively in the stable patient and Fragmin (low-molecular-weight heparin) for 24 hours preoperatively and 3–4 days postoperatively. We give dexamethasone injections or oral prednisolone at physiological doses (see below) perioperatively. In four cases to date using this protocol, none has been lost to thromboembolism. It has been suggested to use o,p'-DDD or ketoconazole (which inhibits steroid biosynthesis) to stabilize surgical candidates preoperatively (Feldman & Nelson 2004). Feldman & Nelson also report the use of combinations of dexamethasone, heparin, plasma and hetastarch for prophylaxis against thromboembolism.

The hypercoagulable state produced by Cushing's syndrome may be caused in part by (1) an elevation of procoagulant factors, and (2) a decrease in antithrombin (Jacoby et al 2001). Elevations in systemic blood pressure or urine protein : creatinine ratio tend to occur with uncontrolled hyperadrenocorticism (Ortega et al 1996). The hypercoagulable state of Cushing's syndrome is demonstrated by an increase in thrombin–antithrombin complexes (Jacoby et al 2001). Feldman & Nelson (2004) suggest that dogs with increased systemic blood pressure or urine protein : creatinine ratio or decreased antithrombin III may be at greater risk for thromboembolism than 'typical' Cushing's syndrome dogs, and may be a subset of dogs more likely to benefit from preoperative medical management.

In the perioperative postsurgical period, physiological doses of exogenous steroids must be given until the remaining adrenal gland is functioning normally. Antibiotics, pain relief and heparin should be given immediately after surgery.

Medical management

Medical management of hyperadrenocorticism is generally reserved for pituitary-dependent hyperadrenocorticism and metastatic or non-surgical adrenal-dependent hyperadrenocorticism.

- *Trilostane*: trilostane is an inhibitor of the enzyme 3-alpha-hydroxysteroid dehydrogenase and inhibits steroid hormone production. It is currently the drug of choice in the management of PDH and can be used in patients with functional adrenal tumours to provide symptomatic relief.
- *Mitotane (o,p'-DDD)*: this drug has a direct cytolytic effect on the adrenal cortex, causing mitochondrial damage and cell death. It also directly interferes with steroid biosynthesis, and before the availability of trilostane was the treatment of choice for PDH. However, neoplastic cells are more resistant than normal tissues so higher doses are required.
- *Ketoconazole*: this drug has been used in the management of adrenal carcinomas; it inhibits the enzyme 5α reductase.
- *Carboplatin*: in humans platinum-based chemotherapy protocols have been used as second choice agents with a response rate of 33% (Norton 2005). Therefore, for patients with non-resectable or metastatic tumours, carboplatin could be considered. However, the response rate in veterinary patients is unknown.

Adrenal tumours in the cat are rare.

Pheochromocytoma

Pheochromocytomas are rare, catecholamine-producing tumours that develop from the chromaffin cells of the adrenal medulla or (uncommonly) from the sympathetic paraganglia (paragangliomas). The average age on presentation is 11 years, with no sex predilection (Feldman & Nelson 2004). One study showed an increased relative risk in Pulis, Golden Retriever, Airedale, Bassett Hound, Weimaraner, and English Springer Spaniel, although any breed may be affected (McNiel & Husbands 2005).

Pheochromocytomas are functional tumours due to production of the polypeptide hormones adrenaline (epinephrine), noradrenaline (norepinephrine) and occasionally dopamine. Clinical signs vary and over 50% of these tumours are found as incidental findings (Barthez et al 1997, Gilson et al 1994). When clinical signs are present those most frequently recorded are weakness and collapse; other reported findings are anorexia, vomiting, diarrhoea, weight loss, depression, seizures, restlessness, exercise intolerance, lethargy, abdominal distension and PU/PD. All clinical signs are either related to increased circulating catecholamines or directly associated with the presence of tumour. Rarely, pheochromocytomas can develop in extra-adrenal sites, e.g. the vertebral column, where the presenting clinical sign is spinal cord compression (Platt et al 1998).

There are two types of catecholamine receptor, alpha and beta. Hypertension is a common clinical sign in animals with pheochromocytoma due to increased vascular resistance mediated by stimulation of alpha receptors causing vasoconstriction. Stimulation of beta receptors increases heart rate, contractility and conduction velocity. Pheochromocytoma stimulation of beta receptors can cause significant tachyarrhythmia that contributes to hypertension.

Pheochromocytomas can be benign or malignant and are not always secretory. They can be locally invasive with extension into the vena cava, kidneys and liver. Feldman & Nelson (2004) report that most pheochromocytomas that cause clinical signs are larger and therefore readily identified during abdominal ultrasound or necropsy, whereas those found incidentally (without the presence of obvious clinical signs), tend to be small (<1.5 cm) and well demarcated. The converse of this statement is how many obvious,

large adrenal pheochromocytomas are not causing clinical signs, and so are not identified? This is a difficult question to answer.

Diagnostic work-up

Findings on routine blood work are non-specific, with elevated liver enzymes reported in 10–25% of patients (Barthez et al 1997, Gilson et al 1994). Proteinuria has been reported in up to 50% of patients (Feldman & Nelson 2004, Gilson et al 1994). The documented frequency of systemic hypertension (systolic pressure >160 mmHg) has been variably reported to be present in 25–50% (Barthez et al 1997, Feldman & Nelson 2004, Twedt & Wheeler 1984) of patients; this may be due to sporadic rather than constant secretion of catecholamines. Biochemical tests to measure catecholamines in plasma or urine are seldom used because of their limited availability.

Imaging

Contrast-enhanced CT and MRI are the most sensitive imaging techniques for localization and assessment of local invasion and metastasis. Other imaging modalities include plain radiographs that may show a mass or mineralization in the region of the adrenal glands. Caudal vena caval angiography diagnosed a tumour thrombus correctly in 57% of dogs with pheochromocytomas (Gilson et al 1994). Abdominal ultrasound is an effective method of identifying adrenal masses, and is 80% sensitive and 90% specific for the detection of caval thrombi associated with adrenal masses in dogs (Kyles et al 2003).

Staging

Pheochromocytomas can metastasize intra-abdominally (e.g. caudal vena cava, kidney, liver, regional lymph nodes, spleen, pancreas) but can also spread to lung, bone, heart and CNS (Barthez et al 1997). It is important to image thorax and abdomen prior to surgery and if clinical signs are appropriate, further imaging of brain, bone, etc. may be prudent. Another reason to ensure adequate imaging and thorough examination and history taking in these patients is that concurrent neoplasia (54%), including endocrine neoplasia (Barthez et al 1997), may be present.

Treatment

Surgery

The treatment of choice is surgery, i.e. adrenalectomy. Complications are common and, prior to surgery, hypertension and cardiac arrhythmias must be stabilized. Treatment with alpha antagonists, e.g. phenoxybenzamine (at a gradually increasing dose) or prazosin, is required to reduce blood pressure and normalize intravascular volume in individuals with chronic hypertension. Tachycardias and tachyarrhythmias should be treated with beta-adrenergic antagonists such as propranolol or esmolol (to reduce heart rate). Beta-adrenergic antagonists must only be used after prior therapy with alpha-adrenergic drugs, because giving beta-blockers alone would reduce heart rate in the presence of unopposed tumour-induced hypertension, which may lead to a hypertensive crisis (Young & Landsberg 1998). When possible, patients should be treated for 1–2 weeks before surgery. Pre-treatment with such drugs reduces perioperative mortality from 40% to less than 20% (Barthez et al 1997, Gilson et al 1994, Kyles et al 2003).

Anaesthetic agents that precipitate arrhythmias (e.g. morphine and ketamine) should be avoided. Premedication with benzodiazepines (e.g. diazepam) is preferable to phenothiazines (e.g. acepromazine) and induction with propofol is preferable to barbiturates. Intraoperatively, manipulation of the tumour can cause dramatic fluctuations in blood pressure, tissue oxygen saturations, heart rate and rhythm. These parameters should be monitored closely. Drug therapy such as propranolol and dobutamine may be required intraoperatively, as well as modifications to intravenous fluid therapy and the use of colloids. Given that the histological diagnosis of pheochromocytoma versus adrenal carcinoma is not known until after surgery, the surgeon may elect to give physiological doses of dexamethasone perioperatively, especially in the absence of clinical signs consistent with pheochromocytoma.

After adrenalectomy, hypovolaemia may occur due to reduction in catecholamine concentrations. Crystalloids should be used to manage hypotension. These patients may require ICU nursing for a number of days after surgery.

For patients who survive the postoperative period the MST was 15 months in one study (McNiel & Husbands 2005) and Barthez et al (1997) reported a range from 1 day to 3.5 years.

Chemotherapy

Chemotherapy has not been evaluated in the management of pheochromocytomas. For patients with non-resectable disease, medical management is aimed at managing hypertension and cardiac arrhythmias. Human patients with metastatic disease have been treated with protocols combining vincristine, cyclophosphamide and dacarbazine.

Radiotherapy

The role of radiotherapy is not known. Of concern is the low normal tissue tolerance of kidney tissue to radiation.

Tumours of the pituitary gland

Pituitary tumours are one of the most common intracranial tumours seen in the dog. Up to 85% of dogs with Cushing's syndrome have pituitary-dependent hyperadrenocorticism (PDH) (Feldman & Nelson 2004). The majority of dogs with PDH have a functional tumour of either the pars distalis (80%) or pars intermedia (20%) of the anterior pituitary.

These tumours are usually small (<1 cm) and rarely cause clinical signs other than endocrine imbalance. A pituitary macroadenoma is described as a pituitary tumour >1 cm in diameter and not all of these tumours are hormonally active. In some patients that have been previously diagnosed with PDH, neurological signs will develop months to years after diagnosis, whereas in other patients neurological signs are the first indication. The neurological signs are consistent with hypothalamic disturbance, including propulsive and constant pacing, behaviour changes and loss of vision.

Diagnostic work-up

A CT or MRI (**Figure 26.5**) is required for diagnosis. The authors would advise a CT/MRI in any patient with PDH to ensure that no macroadenoma is missed.

Treatment

For PDH caused by a pituitary microadenoma (i.e. no pituitary mass visible on CT or MRI scanning), conventional therapy is medical management as previously discussed under adrenal tumours.

Radiotherapy

For PDH where a pituitary mass is visible on CT or MRI scanning, the treatment of choice is radiotherapy with a good prognosis in patients with no or only mild neurological signs (Théon & Feldman 1998) (see **Figure 26.5**). In this study patients were given a total dose of 48 Gy (4 Gy/fraction, three times weekly). For patients with mild neurological signs the mean and median progression-free survival (PFS) was 20 ± 3.5 and 21 ± 2.8 months, respectively; for dogs with more severe neurological signs mean and median PFS was 17 ± 3 months and 13.1 ± 8 months, respectively. Dogs with non-secretory tumours had a significantly worse prognosis than those with secretory tumours. In this study, 12.5% of dogs did not complete treatment due to progressive clinical signs.

These results emphasize the importance of early diagnosis and treatment. The smaller the tumour is at diagnosis, the better the neurological status and expected efficacy of radiotherapy.

Surgery

Hypophysectomy is performed by a trans-sphenoidal approach and should only be performed at a specialist institution. Meij et al (2002) reported on 84 dogs that underwent the procedure; 6 dogs died shortly after surgery, 6 dogs had an incomplete resection and the overall response rate was 86%. Only dogs with relatively small tumours (up to 10 mm in diameter) were considered candidates for surgery.

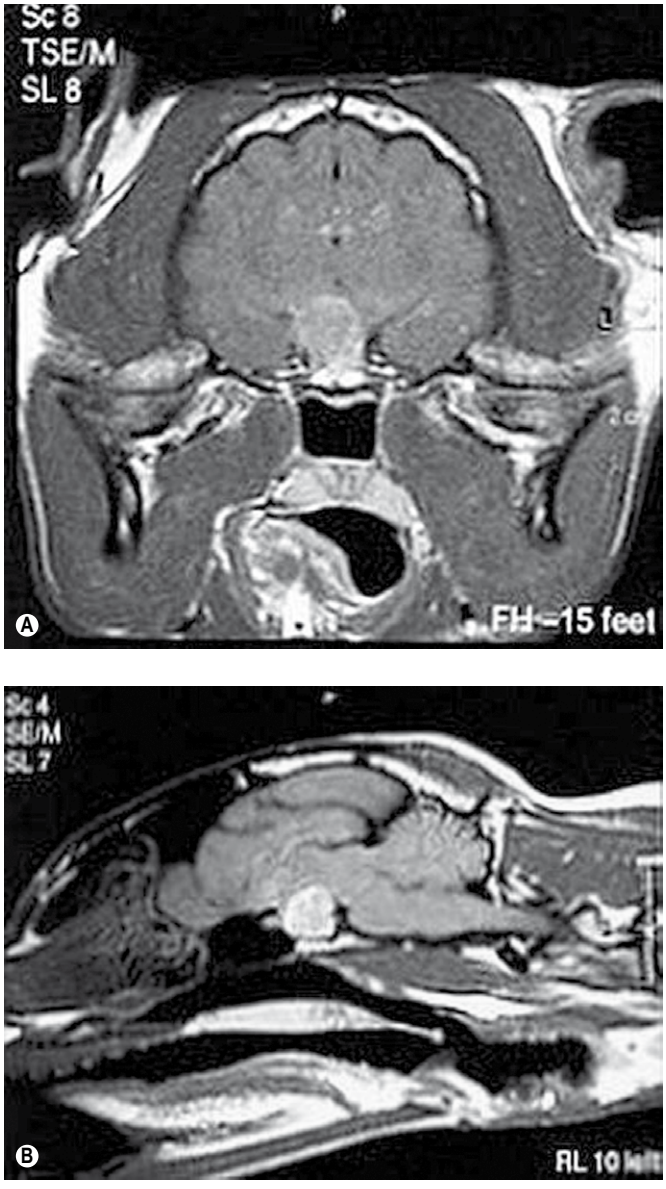

Figure 26.5 MRI scan of a canine pituitary macroadenoma.

Tumours of the ovary and testes

See Chapter 17.

FELINE TUMOURS

Thyroid tumours

The most common tumour of the feline thyroid gland is the functional adenoma (or adenomatous hyperplasia) leading to hyperthyroidism. Carcinomas, although seen, are rare and account for <2% of hyperthyroid cats (Guptill et al 1995, Petersen & Becker 2005, Turrel et al 1988). Feline thyroid carcinomas are locally invasive and metastasis to regional lymph node and lung is common (Cook et al 1993, Turrel et al 1988).

Hyperthyroidism is the most commonly diagnosed feline endocrine problem and one of the most commonly diagnosed conditions in veterinary practice. The aetiology is currently unknown. The typical patient is an older (>8 years of age) feline with a history of weight loss and polyphagia (Peterson et al 1983).

Clinical signs

Typical signs include weight loss, polyphagia, hyperactivity, vomiting, diarrhoea, anorexia and dyspnoea.

Physical examination

Signs of recent weight loss, heart murmur or tachycardia and a palpable thyroid nodule are suggestive of a thyroid tumour/hyperplasia. Other differentials for a mass located in the ventral neck include lymph node enlargement, parathyroid hyperplasia or neoplasia.

Diagnostic work-up

A number of diagnostic tests are advised for cats with suspected hyperthyroidism, including total T4, biochemistry, haematology, urinalysis and thoracic radiographs. About 90% of cats with hyperthyroidism have an elevated total T4 (Thoday & Mooney 1992); 50% of cats with hyperthyroidism have radiographic evidence of cardiac enlargement.

Over 90% of cats have elevations in one or more of the following liver enzymes: alkaline phosphatase (ALKP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and

aspartate aminotransferase (AST). Approximately 20% of cats are azotaemic (Turrel et al 1988). In cats, T4 is the main secretory product of the thyroid gland, although T3 is the more potent hormone.

Treatment

Medical management

Methimazole and carbimazole are oral thioureylene drugs used in the management of cats with hyperthyroidism by interfering with the production of thyroid hormones. They manage the symptoms of hyperthyroidism resulting from a secretory tumour but do not affect the tumour/hyperplastic tissue directly. Daily medication is required to continually correct the thyrotoxicosis.

Treatment of hyperthyroidism in cats can worsen renal function (Graves et al 1994). These drugs can be withdrawn after a trial course if renal parameters deteriorate with treatment, as renal failure is a much greater risk to life than hyperthyroidism. Side effects include vomiting and inappetence; more rarely cytopenia and hepatopathies may develop. These drugs can be used to control thyrotoxicosis to stabilize cats prior to therapy with ^{131}I or surgery.

Iodine-131 (^{131}I) treatment

Radioactive iodine will successfully ablate hyperactive thyroid tissue and is the most effective treatment for feline hyperthyroidism. However, availability and the time the patient needs to be in isolation may affect a clients' decision to choose this treatment option. In one large study (524 cats) the MST was 24 months (Peterson & Becker 1995) with 1-, 2-, 3- and 4-year survival at 89%, 72%, 52% and 34%, respectively.

Surgery

When possible, oral medication should be given for 6–12 weeks prior to surgery to allow improved status for anaesthesia and surgery (Feldman & Nelson 2004). A beta-blocker such as propanolol can be given for severe tachycardias and supraventricular tachyarrhythmias. Intravenous fluid therapy should be given below maintenance rates just prior to and during surgery to avoid fluid overload. Atropine, xylazine and ketamine are to be avoided.

Thyroidectomy is a relatively simple, quick and often curative procedure. It is estimated that 70% of hyperthyroid cats have bilateral disease, thereby requiring bilateral thyroidectomy. Bilateral removal of the parathyroid glands will result in hypoparathyroidism and hypocalcaemia, so care should be taken to preserve some normal parathyroid tissue. As long as some parathyroid tissue remains, postoperative hypocalcaemia should be mild and transient. One surgical approach to avoid iatrogenic hypoparathyroidism is to perform an extracapsular thyroidectomy for unilateral disease and one extracapsular thyroidectomy and one intracapsular thyroidectomy for bilateral disease (Straw R, personal communication). In cats having unilateral thyroidectomies there is the possibility of hyperthyroidism returning due to the development of disease in the remaining lobe.

Tumours of the parathyroid glands

Primary hyperparathyroidism is rare in the cat. Of the few reports in the literature the mean age was 13 years.

Pituitary tumours

The reported incidence of pituitary tumours in the cat is low but possibly under-reported. The majority of patients with pituitary tumours have functional macroadenomas; carcinomas are seen less frequently.

These tumours typically arise from the somatotrophic cells of the pars distalis of the anterior pituitary gland and secrete growth hormone (GH). The majority of cats are diabetic by the time acromegaly is diagnosed due to the catabolic and diabetogenic effects of GH and the anabolic effects of insulin growth factor-1 (IGF-1). In general, cats with pituitary gland tumours have been treated unsuccessfully for diabetes for weeks to months before further diagnostics are implemented to define the presence of a pituitary tumour.

Clinical signs

These are often consistent with diabetes mellitus (i.e. PU/PD, polyphagia, weight loss, muscle weakness) but can also include clinical signs consistent with acromegaly (**Figure 26.6**): soft tissue hypertrophy and bone remodelling resulting in large head and body size; respiratory stridor caused by thickening of pharyngeal tissues, and cardiomegaly and renomegaly that may result in heart or renal failure. Presenting signs may also be consistent with a space-occupying lesion, leading to depression, disorientation and potentially seizures.

Diagnostic work-up

For any cat with insulin-resistant diabetes and/or clinical signs of acromegaly, serum IGF-1 should be measured. Serum IGF-1 levels reflect GH levels in humans and provide a good screening test for feline patients (Berg et al 2007). In cats with a suspected pituitary macroadenoma, advanced imaging (CT/MRI) is required for diagnosis.

Treatment

Treatment options for patients with a pituitary macroadenoma are medical management (not effective), hypophysectomy and radiotherapy.

Surgery

Trans-sphenoidal hypophysectomy has been reported in a small number of cats (Meij et al 2001, 2002). However, as

Figure 26.6 The typical appearance of an acromegalic cat.

only a very small number of neurosurgeons are carrying out this procedure, the recommended treatment of choice for the majority of feline patients is radiotherapy.

Radiotherapy

Pituitary macroadenomas are radiation sensitive and a number of protocols have been reported in the literature with total doses up to 5400 cGy (**Figure 26.7**). MST was 17 months with improvement in endocrine signs seen 1–5 months after completion of treatment (Kaiser-Hotz et al 2002, Mayer et al 2006).

Prognosis

Cats with no neurological signs have a better long-term prognosis than those with neurological signs at the time of starting therapy, although in most instances neurological signs improve within 1–2 months of starting treatment. The other point to bear in mind is that although endocrine signs improve after radiotherapy, this is not immediate. Patients that are significantly compromised due to ongoing diabetes or the clinical effects of GH are unlikely to have as good an outcome as patients that have the condition diagnosed earlier. It is important to recognize these patients early and refer for appropriate therapy, as survival times in excess of 2 years are possible.

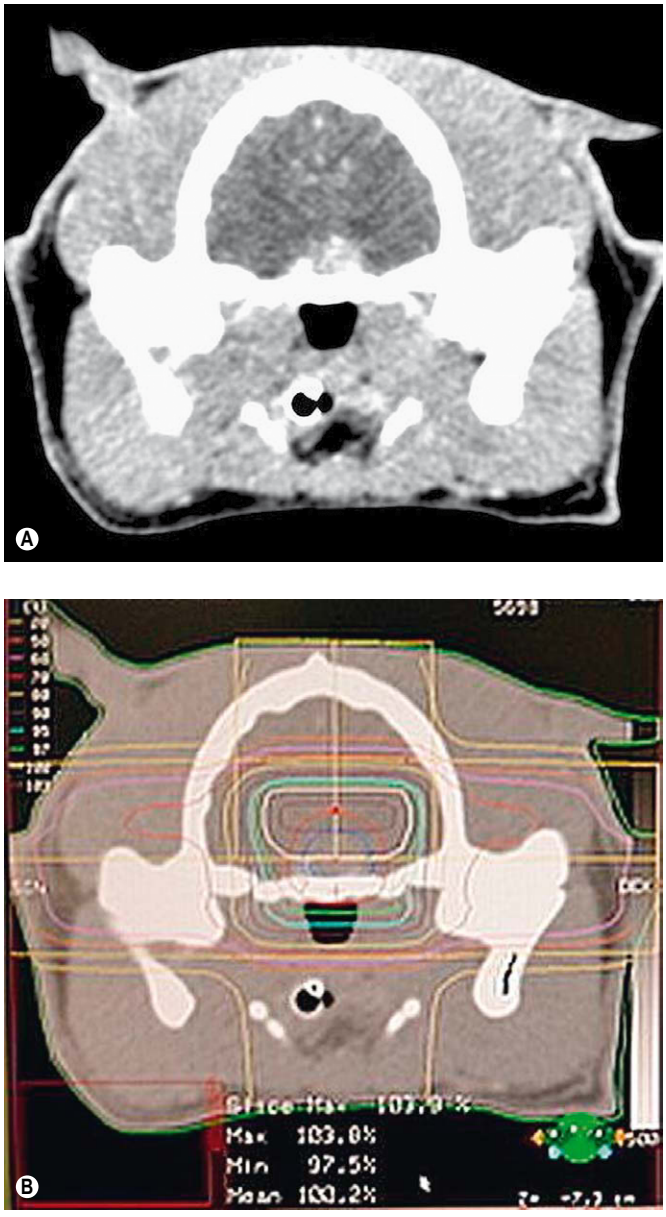

Figure 26.7 (**A**) CT of and (**B**) radiotherapy plan for a cat with a pituitary macroadenoma.

Tumours of the ovary and testes

See Chapter 17.

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CHAPTER 27

Future directions

It is always good to look forward, and certainly veterinary oncology is an exciting and dynamic field in which to be working. We have learnt a great deal in the last 30 years and now the identification of a lump is not an automatic death sentence for a veterinary patient. Our knowledge of oncological surgery, chemotherapy and radiotherapy continue to provide hope for clients seeking the best for their canine and feline companions. As we improve what we have to offer to our veterinary patients, we can also look to what our human colleagues are working on and how that may spin off to benefit our patients.

It has now become accepted that the cancers which affect our canine companions have similarities to some of the same cancers that afflict humans. This has been shown most clearly in canine osteosarcoma and has prompted joint research ventures that will benefit both human and veterinary patients. What could be more appropriate than cementing the bond between humanity and dogs than by studying the diseases that affect them both to their mutual benefit!

The sequencing of the canine genome and the advances in canine cytogenetics offer a unique opportunity to explore the genetic basis for many canine cancers that primarily affect certain breeds (e.g. osteosarcomas and Rottweilers, sarcomas and Flat-Coat Retrievers, gliomas and mast cell tumours and Boxers, etc.) (Breen 2008). Identifying genes in these breeds may ultimately allow identification of similar genes in humans, but in the meantime will hopefully enable these genetic weaknesses to be bred out of our pure-breed dogs.

Dysregulation of many oncogenes has been associated with the development of many human cancers. The recent identification of one of these, the MET proto-oncogene in a large percentage of Rottweilers compared to other breeds, supports the belief that germline mutations contribute to the high rates of cancer in a similar manner to inheritable cancer in humans (Liao et al 2006). Modiano et al (2005) evaluated breed predisposition in the development of B- and T-cell lymphomas and were able to demonstrate that certain breeds were more likely to develop T-cell rather than B-cell disease.

Telomere length and the rate of telomere loss are similar in both humans and dogs, which means that drugs targeted at telomerase, one of the main mechanisms by which cancer cells achieve immortality, can be developed using naturally occurring tumours in dogs to define new strategies that will benefit both species (Cadile et al 2007).

The early diagnosis of cancer is vital to successful treatment and throughout this book we have emphasized how important it is to recognize signs early and set up the appropriate diagnostics and treatments. In veterinary medicine there is much we can improve on by the simple process of thorough physical examination, simple diagnostics such as fine needle aspirates and biopsies, and talking with specialists as to the best approach for patient management. One spectacular improvement is the enhanced availability of advanced imaging in the form of CT/MRI that facilitates improved staging, treatment planning and prognostic evaluation, etc. for our patients. These tools have been available to our human colleagues for a number of years and all contribute to improved survival time for patients.

The hunt for 'serum markers' of malignancy that are specific for individual cancers continues to be an active area of research that has come a long way since the identification of CA-125 and its association with ovarian cancer in women (Nossov et al 2008). The hope is that a simple blood test can be developed to screen for cancer and therefore facilitate early diagnosis. Such tests would also be potentially valuable in monitoring response to treatment and tumour recurrence. In humans, prostate-specific antigen has been a valuable tool in the early detection of prostatic carcinoma in men (Diamandis 1998), but a similar test in male dogs did not show the same specificity (Bell et al 1995).

Proteomics research does have the potential in the future to provide new screening methods for veterinary cancers; the major problem with the technology presently is determining the specificity of the tests (Jackson et al 2007, McCaw et al 2007) and further investigations are required (Gaines et al 2007). Currently, one serum marker that is routinely used to assess response to treatment in veterinary patients is hypercalcaemia, a common paraneoplastic syndrome, that when present is, in many cases, a valuable marker of tumour burden in patients with lymphoma and anal sac adenocarcinoma. Interestingly, in some patients, treatment selects tumour cells that no longer produce parathormone-like factors, making this method of monitoring these patients not always reliable.

Enhancing the immune system in the fight against cancer has always seemed to make intellectual sense; however, it has proved to be much more difficult than was previously thought. There have been a few tantalising breakthroughs in human oncology that have been sufficient to continue research in this area. Active research has certainly led to a more in-depth understanding of the complexity of how the immune system works, with the anticipation that an immunological approach, in conjunction with standard treatments (multimodality treatment), will result in improved survival times for patients with cancer.

In veterinary medicine the development of the melanoma vaccine (Bergman et al 2006) has been the most promising

development in the treatment of canine melanoma since the availability of radiation to control local disease. Other interesting developments along the lines of tumour vaccine include the recent report on the development of an allogeneic haemangiosarcoma tumour lysate vaccine (U'Ren et al 2007). Although the vaccine elicited a good humoral response in dogs with haemangiosarcoma, further trials are required to determine a survival benefit to the vaccine. This vaccine was given concurrently with doxorubicin and as such was not intended as sole treatment, but rather worked in a complementary fashion to chemotherapy.

Cytokines are a further arm of the immune system that potentially can be utilized in the treatment of cancer patients. Interleukin-2 (IL-2) has been used in human patients with renal carcinoma (Klapper et al 2008), and inhalant IL-2 showed some promise for canine patients with pulmonary metastases (Dow et al 2005). Jourdier et al (2003) looked at the effect of IL-2 on feline fibrosarcomas. In this study patients were given intratumoral injections of a recombinant poxvirus expressing IL-2. Sixty-one per cent of cats treated with surgery and iridium radiotherapy had recurrence over a 12-month period, whereas only 28% of cats given immunotherapy as part of treatment had local recurrence. Interferons (IFNs) are also currently under investigation in the management of feline sarcomas (Hampel et al 2007).

Targeting tumour vasculature with anti-angiogenic drugs or metronomic drug regimens is another area of recent advance. Angiostatin research is ongoing in a number of canine and human cancers (Pirie-Shepherd et al 2002).

New classes of drugs, for example, the tyrosine kinase inhibitors, are currently being evaluated as to their efficacy in a number of feline (Lachowicz et al 2005) and canine (Gleixner et al 2007) cancers. New methods of delivery via liposome encapsulation are also under investigation as a means of increasing drug delivery to target organs without increasing toxicity; currently the most widely available of these drugs is liposome-encapsulated doxorubicin (Doxil) (Sorenmo et al 2007).

With all these new developments in the treatment and detection of cancer becoming available to veterinary surgeons, it is important to remember that the first step in the successful treatment of a patient with cancer is the diagnosis, and that process starts in the consulting room with a thorough history taking and physical examination. The next step is the appropriate diagnostic evaluation of the patient. This means a good understanding of the biological behaviour of cancer and a rational approach to the work-up. Doing every test available is not the way to work up a patient and may dissipate valuable financial resources that could otherwise be channelled into treatment; multiple tests are not an excuse for bad medicine.

The next step is that if you are not qualified to carry out treatment, do not do so without discussing referral options with your client; the veterinary specialist is not there to salvage bad work, but rather to use their specialized knowledge to ensure the best possible outcome for the patient. Not every client wants or can afford referral, but it should be their decision. If you find yourself dealing with a case that cannot go for referral, do not hesitate to contact a specialist for advice and support.

Cancer is not ready to be beaten yet, but the strides that have been made in what we have to offer our veterinary patients is truly amazing and will continue to be so.

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