Every effort has been made to ensure that the drug dosage schedules within this text are accurate and conform to standards accepted at time of publication. However, as treatment recommendations vary in the light of continuing research and clinical experience, the reader is advised to verify drug dosage schedules herein with information found on product information sheets. This is especially true in cases of new or infrequently used drugs.

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Series Preface

The Practical Veterinarian series was developed to help veterinary students, veterinarians, and veterinary technicians quickly find answers to common questions. Unlike larger textbooks, which are filled with detailed information and meant to serve as reference books, all the books in The Practical Veterinarian series are designed to cut to the heart of the subject matter. Not meant to replace the reference texts, the guides in this series complement the larger books by serving as an introduction to each topic for those learning the subject matter for the first time or as a quick review for those who have already mastered the basics of each subject.

The titles for the books in our series are selected to provide information for the most common subjects one would encounter in veterinary school and veterinary practice. The authors are experienced and established clinicians who can present the subject matter in an easy-to-understand format. This helps both the first-time student of the subject and the seasoned practitioner to assess information often difficult to comprehend.

The editor and authors hope that the books in The Practical Veterinarian series will meet the needs of readers and serve as a constant source of practical and important information. We welcome comments and

suggestions that will help us improve future editions of the books in this series.

Shawn P. Messonnier, D.V.M.

Preface

Veterinary Oncology represents a brief review of the practical aspects of veterinary medical oncology. As many of my close friends know, I hate cancer but I love oncology. I hope you find the information within this text as helpful in your practice as I have found it in mine. The information presented comes from a collection of lecture notes, handouts, and seminars that I presented or attended over the past 15 years. During this short career, I have learned two principles that should be passed on to every medical oncologist or veterinarian practicing medical oncology. The first is "when in doubt, check it out." This means get a diagnosis and avoid the wait-and-watch-it approach—this is a wait-and-watch-it-get-worse approach. The second principle is "measure twice, cut once." There are so many places for making math errors when prescribing chemotherapy. As I tell my sons, "you can never unpeel a banana" (my residents hate my quotes). I hope you find the following information helpful in your practice of veterinary medical oncology.

K.A.H.

Acknowledgments

Thanks to all the folks at Butterworth–Heinemann. I wish The Practical Veterinarian series continued success, and I know it will become a continued resource for veterinary students and veterinarians alike. I would like to thank the doctors and staff of Gulf Coast Veterinary Specialists for their encouragement and teamwork; it's a great place to practice veterinary medicine.

I would like to thank the many pet owners and their pets that I've come to know over the years. The love they share with me and my staff means so very much. I would like to thank the support of my wife Lisa, who, as a former oncology technician, is very understanding of the emotional burden we carry with us every day as we care for the family who has a pet with cancer. Finally, I would like to thank my sons Evan, Erick, and Bryan who keep me young at heart and light as a feather. They are the reason I wear a smile on my face every day (and whistle Disney tunes).

1

Three Rules for Managing the Cancer Patient

RULE 1: Get a Diagnosis

Biopsy, biopsy, biopsy. A veterinarian can never give an accurate assessment (prognosis) or develop an appropriate treatment plan for the tumor-bearing pet without a complete diagnosis. Knowing the histologic type of tumor gives the veterinarian a sense of the natural behavior of the tumor (how it will grow, where it will go).

RULE 2: Evaluate the Entire Patient

Remember, there is a pet attached to the tumor. Many times we forget the *big picture*. A thorough evaluation of

the pet includes obtaining appropriate laboratory information (blood counts, blood chemistry, urinalysis) and surveying radiographic images of the thorax, abdomen, and the tumor site. Additional information may be required, depending on the known natural behavior of the tumor (remember that biopsy you took in rule 1—it is extremely important). These tests may include a bone marrow aspirate, electrophoresis of serum or urine, buffy coat smears, more biopsies, ultrasound of a body area, nuclear imaging, serology, virology, or many other procedures. A thorough knowledge of the entire patient is necessary *before* an appropriate therapeutic plan can be presented. The goal is to identify or rule out the presence of concurrent illnesses and tumor metastases to regional lymph nodes or other body tissues (lungs, liver, skin, bone, for example). This information is essential not only for treatment planning but also to determine treatment success or failure.

RULE 3: Develop an Appropriate Treatment Plan

Determine your goal. Is curing possible or should more emphasis be placed on quality of life or can both be achieved? In general, three choices face every family with a tumor-bearing pet.

Choice 1: What Is Best for the Cancer?

In today's world there are basically two ways to treat cancer: remove the tumor with surgery and getting cancer-free edges all around the tumor or destroy the tumor's ability to grow, using radiation, chemotherapy, or both, maybe in combination with surgery. A number of other innovative strategies are under development, such as immune stimulants, nutriceuticals, and tumor vessel growth inhibitors, but their true ability to control cancer is not yet known or proven, nor the best way to use them in managing cancer patients, human or animal.

Veterinarians cure a large majority of cancers with surgery. Those that cannot be completely removed and have not yet spread to other body sites can be cured with additional measures—radiation, chemotherapy, and the like—no differently than in people. Common concerns are how a pet will look without a leg, a lower jaw, or a rib, how much radiation therapy costs, and what the side effects are. Every pet owner whose loved one has cancer faces these and other questions. There are no easy answers. However, if the objective of the planned treatment is to attempt to cure the cancer, surgery, with or without radiation, has to be strongly considered. Talk to a veterinary oncologist!

Choice 2: What Is Best for the Pet?

Remember, for most families, the quality of life for their pet is more important than the pet's remaining quantity of life. Remember, cancer is uncontrolled growth. If the abnormal growth cannot be removed from the body or controlled with localized radiation therapy, it is entirely appropriate to use medications, such as anticancer drugs, nutritional supplements, pain control medications, anticough or antinausea medications, to maximize the quality of life of the cancer-bearing pet. To control the uncontrolled growth of cancer, anticancer drugs (chemotherapy) are used. The goal of chemotherapy is not to cure the cancer but to slow down the growing phase of the cancer. Yes, many cancer cells are killed with chemotherapy and tumor shrinkage can be observed; however, it is impractical in most situations to expect that every cancer cell will be killed by any chemotherapy protocol or strategy. With chemotherapy, the more drugs used and the more often they are given, the more cancer cells are killed. Therefore, to significantly decrease the burden of cancer and increase the lifespan of the pet, combination chemotherapy protocols that prescribe drugs every 2, 3, or 4 weeks throughout the remaining lifespan of the pet should prolong the pet's survival. Obviously, most chemotherapy drugs do not know a normal cell from a cancer cell; therefore, more drugs given often results in the possibility of more side effects. If the goal is to provide better quality of life than more quan-

tity of life, a fewer number of drugs at lesser doses given less often will still slow down cancer, just not as much.

Choice 3: What Is Best for the Family?

It is entirely appropriate not to treat cancer in pets. In fact, in some situations, we should not recommend cancer therapy. However, just because we are not controlling the cancer does not mean we cannot provide the pet a comfortable life. When this cannot be accomplished, we should strongly urge pet owners to consider the choice of euthanasia. It is important to have a support group during this process. Please rely on the good advice of family and friends during this difficult time. In addition, many pet owners are willing to share their positive and negative experiences. It is essential to provide adequate nutritional support, pain control, and other measures that ensure the pet's good quality of life. Quality of life is very subjective. Everyone has an opinion. Ask for opinions and listen to them. Then, make your best choice. Hindsight is 20:20, but if you follow the preceding rules—get a diagnosis and evaluate the whole patient—you should have plenty of information to make the best choice available at that time.

I hope this book provides some insights toward my approach in managing the veterinary cancer patient. Always consult with a board-certified veterinary oncologist. Use a team approach and allow the pet owners to participate in the team. Cancer is a battle that can be

won—engage in the fight but realize when it is time to retreat.

2

Getting a Diagnosis

Fine-needle Aspiration

Fine-needle biopsy is a powerful diagnostic tool that has very good client (and patient) acceptance because it is minimally invasive. A good biopsy technique widens the applications and increases diagnostic yield.

Technique

STANDARD ASPIRATION TECHNIQUE Attach a 22-gauge needle (length variable depending on depth of lesion aspirated) to a 12-cc syringe. Localize and immobilize the lesion by manual palpation or with ultrasound guidance. Introduce the needle into the lesion and apply negative pressure by repeatedly (three to five times)

pulling back on the plunger of the syringe. If the lesion is large enough, redirect the needle, without withdrawing it, into various areas of the lesion. Release all negative pressure, and then withdraw the needle from the lesion. Quickly remove the needle from the syringe, fill the syringe with 8–10 cc of air, reattach the needle to the syringe, and expel the material within the needle onto a clean glass slide by rapidly depressing the syringe plunger. Quickly prepare smears as described later.

CAPILLARY ACTION (NONASPIRATION) TECHNIQUE This technique is easier to perform and yields results equally diagnostic to the standard aspiration technique. It may provide samples with less blood contamination, especially in more vascular lesions or lesions that do not typically exfoliate cells readily (mesenchymal tumors). Attach a 22-gauge needle (length variable depending on depth of lesion aspirated) to a 12-cc syringe that has been prefilled with 10 cc of air. Localize and immobilize the lesion by manual palpation or with ultrasound guidance. Move the needle through various areas of the lesion repeatedly (five to eight times, do not aspirate). Withdraw the needle from the lesion and expel the material within the needle onto a clean glass slide by rapidly depressing the syringe plunger. Quickly prepare smears as described later.

TRU-CUT BIOPSIES To perform Tru-cut biopsies, make a small puncture in the skin overlying the lesion with an 11

blade. Semiautomated and fully automated instruments should be spring-loaded prior to introducing the needle into the lesion. Introduce the needle, specimen notch closed, into the lesion, leaving enough room for the needle to travel 1.5–2.0 cm forward, depending on penetration length of needle, and still remain in the lesion. Then, obtain the biopsy specimen as follows:

- *Manual Tru-cut.* Advance the caudal portion of the handle of the needle forward to open the specimen notch, then advance the cranial portion of the needle handle forward to close the specimen notch and obtain the biopsy. Always move in a forward direction. Remove the needle and specimen.
- *Semiautomated.* Advance the caudal portion of the handle of the needle forward to open the specimen notch, then firmly depress caudal portion of the handle of the needle farther forward to complete biopsy procedure. Remove the needle and specimen.
- *Fully automated.* While holding the apparatus still, depress firing button to obtain the biopsy. Remove the needle and specimen.

Sample Preparation and Handling

GENERAL COMMENTS Always obtain several samples from various sites within each lesion. This optimizes the chance of achieving a diagnosis. Single aspirates or biopsies may be nondiagnostic for various reasons, such as

missing the lesion, sampling a nonrepresentative or necrotic area of the lesion, or blood contamination during sampling. Make several slides to examine, especially if slides are to be submitted to an outside lab for evaluation, because labs charge by the lesion not by the number of slides submitted. Keep slides for cytological evaluation away from formalin fumes and formalin-fixed tissues. Formalin partially fixes cells on microscope slides, which results in poor slide staining and nondiagnostic samples. This occurs during both slide preparation and shipping; do not mail unstained slides and formalin-fixed tissues in the same package. When sending slides to an outside lab, use Styrofoam or plastic mailers (flat cardboard mailers often result in broken slides), provide a thorough history (including drug therapy) and problem list, and call the lab to discuss results if they are unusual or unexpected.

FLUID FOR ANALYSIS All fluid for analysis should be collected in EDTA to prevent coagulation and help preserve cells. Non-EDTA specimens usually cannot be interpreted. A portion of the fluid can be retained in a sterile tube if culture and sensitivity are desired. If using an outside lab, it is helpful to prepare a few slides to ship along with the EDTA fluid sample, in case cells degenerate or microbial overgrowth occurs in the sample prior to it arriving at the lab. Again, do not fix cells with ethanol (or formalin) unless the laboratory with which

you deal uses a trichrome or other Papanicolaou-type stain; most do not.

SLIDE PREPARATION Use only clean, new slides when making smears or imprints. Reused slides, even if thoroughly cleaned, usually have surface changes and residues that result in uneven spreading and altered staining characteristics. The two most common techniques for preparing specimens are obtained by fine-needle aspiration of fluid or tissue. Tissues obtained by surgery or from biopsy instruments can be squashed if very small or gently blotted on several areas of or rolled across a slide. Blotting a biopsy sample to remove blood prior to making imprints enhances the diagnostic quality of the slide. Whatever technique is used, rapid drying of slides by waving them in the air or using a hair dryer set on low helps fix the cells to the slide and preserves cell morphology.

Cytologic Criteria for Malignancy

Cytologically, neoplasia is characterized by the presence of a monomorphic population of cells that appears to have come from the same tissue of origin. This is best appreciated by the presence of cells with the same cytoplasmic characteristics. If a neoplasm is diagnosed, two important determinations must be attempted: whether the lesion is benign or malignant and what is the tissue of origin.

Benign versus Malignant

Benign neoplasia or hyperplasia is characterized by a uniform population of cells. There should be a uniform cytoplasmic and nuclear size and shape, uniform nuclear to cytoplasmic (N:C) ratio, and if nucleoli are present, they are of consistent size, shape, and number among individual cells. Malignant neoplasms have nuclear features considered abnormal and indicate a cell population that is growing rapidly and uncontrollably. The following are nuclear characteristics considered to be abnormal: anisokaryosis, pleomorphism, high or variable N:C ratio, increased mitotic activity, nucleoli that vary in size, shape, and number (angular, irregularly shaped nucleoli), coarse chromatin or uneven margination of chromatin at the nuclear membrane, nuclear molding, multinucleation. If many of the cells show three or more of the criteria of malignancy, the tumor is malignant. In the vast majority of the cases, the cytologic criteria of malignancy are accurate predictors of the potential biological behavior of the tumor. However, in some circumstances, and these are the exception to the rule, the cytologic appearance may not accurately predict the biological behavior. A practicing cytologist must be aware of the exceptions to the rule if we are to rely on cytology to provide us with meaningful, accurate information regarding the prognosis of a patient.

Inflammation and Malignancy

The criteria for malignancy are more meaningful if inflammation is not present. Inflammation may cause reactive changes in epithelial or mesenchymal cells that mimic malignancy. Therefore, the criteria of malignancy must be interpreted with caution if the cell population of a lesion contains a mixed cell population of both inflammatory (neutrophils, eosinophils, lymphocytes, macrophages) and noninflammatory cells (epithelial, mesenchymal, round cells, or neuroendocrine cells). In most mixed cell populations, neoplasia may be suspected; however, the diagnosis must be made from a tissue biopsy and histologic evaluation of the lesion.

Specific Tumor Types and Locations

In addition to the presence of inflammation, there are specific instances where the cytologic appearance of the neoplasm does not correlate well with the biological behavior of the lesion. The location of some tumors and occasionally the specific tumor type must be considered when using cytology to determine the malignant potential of certain neoplasms.

MESENCHYMAL NEOPLASMS Mesenchymal tumors are composed of small to medium cells. Aspirates are usually less cellular than with epithelial tumors and the cells arranged more individually. Cytoplasm is wispy and often spindle shaped, with tags of cytoplasm trailing off in one

or two directions from the nucleus. Cytoplasmic borders are usually indistinct. The nuclei are typically oval to polygonal. Malignancies of mesenchymal origin are termed *sarcomas*. The nuclear features of malignancy are usually reliable indicators of the malignant potential of mesenchymal tumors.

Leiomyosarcoma and myxosarcoma are exceptions. *Leiomyosarcomas* and the *myxosarcomas* are uncommon tumors of smooth muscle and fibroblast origin, respectively. These tumors are difficult to differentiate from their benign counterparts (leiomyoma and myxoma) based on cytologic or even histologic features alone. Since some leiomyosarcomas and myxosarcomas have no bizarre nuclear features, histologists often must rely on invasion into surrounding tissues to determine the malignant potential of these tumors. However, if the nuclear criteria of malignancy are met, the lesion is considered malignant. Leiomyomas and leiomyosarcomas typically occur in the GI (gastrointestinal) tract or urinary bladder. The nuclei of these smooth muscle cells have an elongated, cigar-shaped appearance. The cytoplasm is very fragile, and free nuclei are abundant on cytologic preparations. Myxomas and myxosarcomas may occur anywhere in the subcutaneous tissues. The characteristic cytologic feature is an abundant mucinous background that appears cytologically as an amorphous eosinophilic material, similar to synovial fluid. Low to moderate numbers of mesenchymal cells are mixed within the mucin.

The differentiation between sarcoma and reactive fibroplasia associated with inflammation is the primary concern when evaluating mesenchymal tissue. Inflammation can stimulate the production of a reactive population of fibroblasts that are cytologically indistinguishable from sarcoma cells. Therefore, in the presence of inflammation and mesenchymal cells (mixed cell population), the cytologic criteria used to diagnose malignancy are not reliable. Histologic confirmation is required, because in most cases, if inflammation is present, the population of fibroblasts is likely reactive.

EPITHELIAL NEOPLASMS Epithelial tumors are usually composed of large cells. Aspirates are usually very cellular and the cells characteristically exfoliate in clumps or sheets. The cells are round to polygonal with very distinct cytoplasmic borders. They are often tightly adherent to each other with extensive contact between adjacent cells and clear zones between areas of cell junctions. Prominent cytoplasmic vacuolation, signet ring, or acinar formation may be seen if the tumor originates from glandular epithelium. Malignancies of epithelial origin are termed *carcinomas* or *adenocarcinomas*. Unless inflammation is present, the nuclear criteria for malignancy are reliable indicators for the vast majority of epithelial neoplasms. Two notable exceptions, which are actually quite common tumors, are basal cell tumors and perianal or anal gland tumors.

Basal cell tumors are common cutaneous tumors of the dog and cat. They have a site predilection for head and neck. They are the most commonly reported cutaneous tumors of the feline. They have also been called *basal cell carcinomas*, but since they are usually benign, this term does not accurately describe their biological behavior in domestic animals. Cytologically, these tumors contain tight clumps of epithelium with deep blue cytoplasm. They have some nuclear features of malignancy, such as a high N:C ratio, anisokaryosis, and occasional nucleoli. Mitotic figures may be observed occasionally. However, most of these tumors are benign and can be successfully removed surgically. These lesions must be identified as basal cell tumors so they are not mistaken for a malignancy based on the cytologic appearance. The deep basophilic, tightly adherent balls of epithelium with a high N:C ratio in a cutaneous tumor is very characteristic. In addition, low numbers of mature sebaceous gland epithelium may be mixed within the clumps of basal cells. Sebaceous differentiation is associated with some basal cell tumors. This can also aid in the diagnosis. Some basal cell tumors, especially in the cat, contain variable amounts of melanin pigment and must be distinguished from true melanocytic tumors. The cohesiveness of basal cells is a predominant differentiating feature. These tumors grow slowly and rarely metastasize. Surgical excision is usually curative, but recurrence may occur after incomplete excision.

Perianal gland adenomas are benign tumors of the circumanal glands, commonly seen in intact, male dogs >8 years of age. Perianal gland adenocarcinomas do occur, but they are much less common and may be seen in either intact or neutered male dogs. They are seen less frequently in neutered female dogs and rarely in intact females. Perianal gland adenomas are composed primarily of large, polyhedral, hepatoid-like cells, occurring in clumps or clusters. They contain abundant basophilic cytoplasm, often with a pink hue. The N:C ratio is low and nuclei are typically round to oval with clumped chromatin and one or two large nucleoli. This gives the cell a remarkable resemblance to hepatocytes. Most perianal gland adenomas usually contain variable numbers of a second population of smaller epithelial cells with a much higher N:C ratio. These cells are called *reserve cells*. The distinctive population of cells allows easy identification of the tumor; however, the variability of the cell population, along with the prominent nucleoli and clumped chromatin may mimic a malignancy, even with adenomas. In reality, perianal gland adenomas and perianal gland adenocarcinomas are often cytologically indistinguishable. In these tumors, the signalment of the patient plays a major role in determining how to interpret cytologic findings. The vast majority of perianal gland tumors occur in intact males and most of these are adenomas. Some investigators believe there may be a progression of these lesions to adenocarcinomas if not

surgically removed. However, in intact males, most perianal adenocarcinomas do not metastasize, so local recurrence with incomplete excision is about all that happens. In contrast, about half the perianal gland tumors in neutered males and females are adenocarcinomas, and these may metastasize. If a perianal gland tumor is found on a neutered male or female dog or if there is tumor regrowth following surgical removal of a previously diagnosed adenoma on an intact dog, an adenocarcinoma should be suspected. Histology is required.

Anal sac apocrine gland adenocarcinomas are epithelial tumors of the anal sac apocrine glands of the dog. Unlike perianal gland tumors, these tumors are often seen in older, female dogs. Most affected animals have an associated hypercalcemia. This tumor appears as clumps of epithelium with very few distinct cytoplasmic borders. The appearance of free nuclei embedded in a mass of cytoplasm gives this lesion a *neuroendocrine-like* appearance. This allows easy identification by finding a neuroendocrine-like appearance of cells from a mass located around the anus. The cells have a high N:C ratio (lots of nuclei), but the cells are fairly uniform with round nuclei. Occasionally a mild anisokaryosis and sometimes small, indistinct nucleoli can be seen. However, there are usually not enough abnormalities to fulfill the cytologic criteria of malignancy. Cytologically, this tumor usually appears benign; however, the cytological appearance of this tumor does not accurately predict the biological behavior. The N:C ratio is often high but

nuclei are fairly uniform and nucleoli, when present, are indistinct. Even so, it is a malignant apocrine gland tumor. In female dogs, there is a 50% rate of metastasis to regional lymph nodes at time of presentation, 13% in males. In addition, most patients with this tumor have associated paraneoplastic hypercalcemia, which also aids in identification.

ROUND CELL NEOPLASMS Round cell tumors, as a group, share the common cytologic characteristics of being composed of individually arranged, round cells, which usually exfoliate in moderate to large numbers. The cells contain discrete cytoplasmic borders but are not very adherent to each other and contain no junctions between cells. The cytologic criteria of malignancy are not reliable indicators of the biological behavior of round cell tumors. Fortunately, this group of tumors can usually be definitively identified cytologically. The biological behavior then can be considered, based on the tumor type, location, and sometimes cellular differentiation. The six specific round cell tumors are histiocytic tumor, lymphoma, mast cell tumor, transmissible venereal tumor, plasma cell tumor, and melanoma.

Histiocytomas are benign cutaneous tumors of young dogs (usually <3 years of age). The cells contain moderate amounts of pale to lightly basophilic cytoplasm. Nuclei are round to pleomorphic with fine chromatin and indistinct nucleoli. Because these lesions are composed of histiocytes, cells typically display a variable N:C

ratio, pleomorphic nuclei, and anisokaryosis. The tumors frequently become infiltrated with lymphocytes, adding to the heterogeneity of the population. These features may be confused for malignant criteria; however, once identified as a histiocytoma, the diagnosis of a benign neoplasia can be made. Many of these lesions spontaneously regress and surgical removal is curative.

Malignant histiocytosis is the malignant counterpart of the histiocytoma. These tumors may occur anywhere on the body and often invade internal organs. They have significant nuclear features of malignancy and usually show some differentiation toward the macrophage cell line, such as vacuolated cytoplasm, phagocytic activity, pleomorphic nuclei, or multinucleation. The criteria of malignancy are accurate predictors of the biological behavior of this tumor. There appears to be a breed predilection for this tumor in golden retrievers, rotweilers, and Bernese mountain dogs.

Lymphoma, by definition, is a malignancy of lymphocytic origin. Lymphomas are round cell tumors containing individually arranged cells with distinct cell borders. The cells contain scant amounts of deeply basophilic cytoplasm, a very high N:C ratio, and round to polygonal nuclei. The slide preparation often contains small tags of cytoplasmic fragments called *lymphoglandular bodies*. Other cytologic characteristics vary dramatically, depending on the type of lymphoma and the maturity of the neoplastic population. In the dog, most lymphomas are a high-grade malignancy composed of a predomi-

nant population of immature lymphoblasts with nuclei that are 1.5 or more times the size of erythrocytes and one or more nucleoli. However, in the cat, some lymphomas, particularly hepatic and intestinal lymphomas, are composed of small, well-differentiated lymphocytes. These cells have a small mature nucleus approximately the size of an erythrocyte with a small tag of cytoplasm. They are difficult to distinguish cytologically from a normal or reactive population of lymphocytes. Likewise, the anatomic location(s) of the tumor and stage of the disease, along with the cytologic appearance of the cells and any paraneoplastic conditions all affect the prognosis of the patient with regard to expected response to chemotherapy and survival time. Therefore, the cytologic criteria of malignancy play a small role in predicting the overall behavior of this tumor.

Mast cell tumors are composed of individually arranged, round cells with round to polygonal nuclei and variable numbers of purple-staining, small, cytoplasmic granules. All these tumors are considered potentially malignant and, as the saying goes, *never trust a mast cell tumor.* The potential for metastasis and invasiveness is evaluated using two criteria, the cytologic differentiation of the tumor cells and their anatomic location.

Cytologically, mast cell tumors can be classified as well differentiated, moderately differentiated, or poorly differentiated. In general, moderately and poorly differentiated tumors have a much higher tendency to metastasize than well-differentiated tumors. However, some

well-differentiated tumors may be aggressive in their biological behavior. *Well-differentiated* mast cell tumors have high numbers of cytoplasmic granules that often occlude visualization of the nucleus in intact cells. Nuclei are uniform in size and round to oval in shape. *Moderately differentiated* tumors have low to moderate numbers of cytoplasmic granules that usually do not occlude visualization of the nucleus. Anisokaryosis is moderate and there is a variable N:C ratio. Mitotic figures may be seen in low numbers. *Poorly differentiated* mast cell tumors have sparse to no cytoplasmic granules. Anisokaryosis and a variable N:C ratio are frequently observed and may be marked. Nuclei are irregular in shape, and mitotic figures are seen in moderate numbers. An associated eosinophilic inflammatory response may be the key to recognition of an undifferentiated mast cell tumor. The less differentiated the cells are, the greater the potential for invasion and metastasis, regardless of the anatomic location. However, even well-differentiated mast cell tumors may metastasize, depending on the location of the lesion. In the dog, cutaneous mast cell tumors located in the perineal or inguinal regions frequently metastasize, usually to popliteal or abdominal lymph nodes. In addition, mast cell tumors located around the muzzle, in the oral or nasal cavity, or at mucocutaneous junctions frequently metastasize to regional lymph nodes. In these locations, the biological behavior of the tumor cannot be accurately predicted by the cytologic differentiation of the mast cells.

Most cutaneous mast cell tumors in the cat are located on the head and neck (58%). Some cats can develop multiple mast cell tumors. An uncommon, histiocytic form may occur in young cats, <4 years of age. Most cutaneous mast cell tumors in the cat are considered benign. An exception would be the histologically diffuse (vs. compact) or poorly differentiated tumor. Siamese cats appear to have a breed predilection for development of cutaneous mast cell tumors. Systemic mastocytosis occurs in the cat causing mastocythemia and severe splenomegaly with marked infiltration of mast cells. Cutaneous mast cell tumors and systemic mastocytosis are not known to occur simultaneously. An intestinal form of feline mast cell tumor may result in a milder mastocythemia. This disease carries a poorer prognosis than the splenic form.

Transmissible venereal tumors (TVTs) are composed of large numbers of round cells with variable amounts of moderately basophilic cytoplasm. The cytoplasm often contains small punctate vacuoles. Nuclei are round to polygonal with coarse chromatin and one or two large prominent nucleoli. This is the only tumor known to be naturally transmissible. It is transmitted by direct contact and interestingly, does not represent normal dog cells that have become malignant. In TVT cells, the chromosome number is 59. In normal canine cells, the chromosome number is 78, thus TVT cells are cells that have been transformed into cancer cells by passage from dog to dog. It acts somewhat like a parasite, except that

a single tumor cell line causes it. This tumor is usually located in the genital area or nasal cavity (dogs are "nosey"). TVTs can be locally very invasive but rarely metastasize. They are highly sensitive to chemotherapy with vincristine (every 7 days) and gone usually within five or six weeks. The cytologic characteristics of this tumor are useful only in making a diagnosis and have little value in predicting behavior.

Plasma cell tumors, neoplasms of plasma cell origin, are classified as either *extramedullary plasmacytomas* or *multiple myelomas*. Plasmacytomas are lymphoid neoplasms with site predilections for the skin (76%) of the digits and foreleg (32%) as well as the oral cavity (28%), ears, and gastrointestinal tract. This tumor more commonly affects dogs; however, there are reported cases in the cat. In the dog, there may be a breed predilection in airedale terriers (7.7%), boxers (9.4%), and cocker spaniels (11.1%). Plasmacytomas have the cytologic appearance of other round cell tumors with aspirates yielding moderate to large numbers of individually arranged, round to oval cells with discrete cytoplasmic borders. These cells contain variable amounts of deeply basophilic cytoplasm. Many of the cells have a characteristic plasmacytoid appearance with a round nucleus that is often eccentrically located in the cell. This can vary depending on the maturity of the individual cells within the tumor. A perinuclear clear area "Golgi zone" is often seen in the cytoplasm. In the dog, extramedullary plasmacytomas are mostly benign. However, these tumors

often display criteria of malignancy, including marked anisokaryosis, pleomorphism, binucleation, multinucleation, variable N:C ratio, and clumped chromatin. Surgical removal is curative in most cases. Some plasmacytomas in the dog can be locally invasive, resulting in regrowth following surgical removal; and rare reports of metastasis to regional lymph nodes, liver, and spleen have occurred. Extramedullary plasmacytomas in the dog have also been associated with local amyloid production and rarely with amyloidosis, monoclonal spikes, or hypercalcemia. In the cat, these tumors appear to be more aggressive, frequently resulting in monoclonal gammopathies and metastatic disease. However, the biological behavior of this lesion cannot be accurately predicted by the cytologic appearance. The cytologic appearance of plasmacytomas is identical to the appearance of the malignant plasma cell tumor, multiple myeloma, which originates in the bone marrow of dogs and cats. These neoplasms are always malignant, diagnosed by finding greater than 20% plasma cells in the bone marrow of an animal that has other clinical findings consistent with the disease. These include monoclonal gammopathy, hypercalcemia, or lytic bone lesions, particularly in the vertebral column.

Melanomas can occur cutaneously anywhere on the body. However, in the dog they appear to have a site predilection for the oral cavity and digits and are the most common canine oral neoplasm. They frequently are found on the buccal mucosa. This neoplasm is sometimes

included in the group of round cell tumors. Melanomas are similar to mast cell tumors in that the differentiated cells are composed of many cytoplasmic granules and the biological behavior of the lesion depends heavily on the anatomic location as well as cellular differentiation. Cytologic preparations of most differentiated melanomas contain cells that are individually arranged but may cytologically appear to be spindle shaped, epithelioid, or a mixture of both. The cytoplasm often contains variable amounts of fine, brown-black to green-black pigment granules. In contrast to melanocytes, mast cells contain purple granules. Oral melanomas that lack cytoplasmic pigment therefore are classified as amelanotic. However, cytologically small amounts of fine pigment can usually be found even in poorly differentiated tumors. If cells from an aspirated lesion appear very anaplastic and contain both mesenchymal and epithelial features, a malignant melanoma should be suspected. With cutaneous melanomas, the more pigmented tumors are more differentiated and less likely to behave aggressively. Most cutaneous melanomas of the dog are benign, and most well differentiated, cutaneous melanomas are considered benign. However, oral melanomas and melanomas involving the nail bed of the digits are very aggressive. Even well-differentiated (highly pigmented) tumors in these locations are aggressive and metastasize early. The treatment of choice is wide surgical excision or amputation. Melanomas are uncommon tumors in the cat; however, a recent study identified five

types of cutaneous melanomas in the feline: epithelioid, spindle, mixed, signet ring, and balloon cell. The epithelioid, spindle cell, and mixed tumors of the cat are usually pigmented and often found on the ears, forehead, nose, and eyelids. Balloon cell and signet ring types are typically amelanotic. The balloon cell type also usually is found on the head. Cells are large and swollen with cytoplasm, which appears like a balloon. Nuclei display many anaplastic features. The signet ring type is usually found on the shoulder, thorax, and flank areas. The cytoplasm is large and distended with the nucleus pushed off to one side, giving cells a signet ring appearance. Nuclei display many features of malignancy. The signet ring and balloon cell types are believed to be variants of the epithelioid cell type, highly aggressive with metastasis to lymph nodes and several organs. Mean survival time from surgical removal was 4.5 months.

Note: *Melanomas should not be confused with the more common pigmented cutaneous tumor in the cat, the basal cell tumor. Basal cell tumors may contain melanin, but the cells occur in tight, cohesive clusters with a very high N:C ratio.*

NEUROENDOCRINE NEOPLASMS Neuroendocrine tumors are tumors of chemoreceptor or endocrine glands, such as the thyroid, parathyroid, pancreas, or adrenal gland. These tumors share a characteristic cytologic feature. Slide preparations appear as free, round nuclei embedded in a background of cytoplasm, with few distinct cytoplasmic borders visualized. With the exception of

thyroid tumors, which are often bloody, most preparations are very cellular. Knowledge of the malignant potential for each tumor type is important because the cytologic criteria for malignancy are not easily interpreted with these neoplasms. If criteria of malignancy are present, the tumors are likely to metastasize or locally invade surrounding structures. However, nuclei from these tumors often do not display sufficient criteria of malignancy, even when the potential for metastasis or invasion is likely. The most frequently encountered neuroendocrine neoplasm is the thyroid tumor.

Canine thyroid tumors are usually located on the neck or near the thoracic inlet, although some tumors have been identified within the thoracic cavity. There is a breed predilection for boxers, beagles, and golden retrievers. More than 90% of the clinically apparent thyroid tumors in the dog are malignant. Aspirates from thyroid tumors, particularly carcinomas, may contain a large amount of blood contamination. Clumps of epithelial cells may be seen scattered throughout the preparation. These clumps appear as free nuclei embedded in a background of pale blue cytoplasm with infrequent visualization of cytoplasmic membranes or borders. Amorphous pink material (colloid) may be associated with some clumps. Dark, blue-black pigment (tyrosine granules) is sometimes seen in the cytoplasm of epithelial cells. This pigment along with the neuroendocrine appearance of the cells may be used to definitively identify the tissue as

thyroid in origin. Nuclei are round to oval; however, anaplastic features are minimal. Most thyroid tumors, even adenocarcinomas, are composed of a fairly uniform population of cells, displaying few if any criteria of malignancy, even though in the dog most are malignant. Therefore, in the canine, anytime a tumor is identified as thyroid in origin, it must be assumed to be a carcinoma until further confirmation by histopathology. In dogs, hypersecretion of thyroid hormones is uncommon; however, some dogs with adenocarcinomas may be hypothyroid. Adenomas are benign and the prognosis is excellent with surgical excision. Adenocarcinomas are invasive and metastasize if given sufficient time. Prognosis and potential for metastasis depend on tumor size. Dogs with tumors <5 cm in diameter were metastasis free after seven months. Dogs with larger tumors have a 40% chance of metastatic disease at the time of diagnosis.

Note: *Thyroid adenocarcinomas in the dog have been associated with the development of fragmentation hemolysis and disseminated intravascular coagulation* (DIC).

Thyroid tumors in the cat are cytologically identical to those seen in the dog. However, the vast majority of tumors in the cat are benign adenomas or adenomatous hyperplasia and may occur bilaterally. Cytologically, thyroid adenomas, or adenomatous hyperplasia, appear as clumps of epithelial cells scattered throughout the preparation. These clumps contain free nuclei embedded in a background of pale blue cytoplasm with

infrequent visualization of cytoplasmic membranes or borders. Amorphous pink material (colloid) may be associated with some clumps. Dark, blue-black pigment is sometimes seen in the cytoplasm (tyrosine granules). This pigment, along with the neuroendocrine appearance of the cells may be used to definitively identify the tissue as thyroid in origin. Nuclei are round to oval and fairly uniform in size and shape. Adenocarcinomas are uncommon, but it is not possible to cytologically distinguish between adenomas and adenocarcinomas. In the cat, most thyroid tumors are most likely to be benign until proven otherwise; however, histologic evaluation of capsular or lymphatic invasion is often required for a definitive diagnosis. Unlike the canine, most thyroid tumors (adenomas and adenocarcinomas) in the cat actively secrete thyroid hormones. Adenomas are usually well encapsulated and the prognosis is excellent with surgical removal. If bilateral thyroidectomy is performed, the patient must be monitored for signs of hypothyroidism or hypocalcemia, resulting from removal of the parathyroid glands. Adenocarcinomas are locally invasive and metastasize to regional lymph nodes. Metastatic disease was reported in 40–71% of cats with adenocarcinomas.

Blood Smear Evaluation

The evaluation of a blood smear allows the veterinarian to gain rapid, valuable information regarding the health

of the patient when the evaluation is performed in a systematic fashion. Estimating cell numbers and evaluating the morphologic changes in erythrocytes, leukocytes, and platelets can obtain the important clinical information needed for the hematologic evaluation of an animal. The value of these findings, many of which are not recognized by automated cell counters, cannot be overemphasized.

Blood Collection and Slide Preparation

Vacutainer tubes containing EDTA should be filled to the designated amount. Partial filling of vacutainer tubes with blood may cause artifactual changes in cell morphology and numerical values. Blood smears should be prepared as quickly as possible to minimize artifactual changes in erythrocytes and leukocytes, such as red cell crenation, leukocyte vacuolation, and nuclear pyknosis. The coverslip technique for making smears is preferred over the glass slide technique. This technique minimizes traumatic injury to cells during slide preparation. This technique produces more even distribution of cells, allowing more accurate estimation of leukocyte and platelet numbers. Smears should be rapidly dried with a blow drier to eliminate artifacts of air-drying red blood cells. This is particularly important when attempting to identify red cell parasites, such as *Haemobartonella felis*, or evaluation of erythrocyte shape changes.

Systematic Evaluation of a Blood Smear

SCANNING THE SMEAR The first step in the evaluation of a blood smear is to scan the slide using a 10× or 20× objective. With regard to the red blood cells, observe the red cell density and look for the presence of rouleaux or agglutination. (Rouleaux may be differentiated from agglutination by saline test where 1 drop of blood is mixed with 4 drops of saline and observed on wet mounts; rouleaux will disperse with saline dilution.) With regard to nucleated cells, confirm that the mature neutrophil is the predominant cell type. The presence of any left-shifted neutrophils or large or atypical leukocytes, as well as the presence of any nucleated erythrocytes, should be recorded. Platelet clumps should also be identified at this magnification, because they affect how platelet numbers are interpreted later in the evaluation. Leukocyte numbers may be estimated using the following formula:

$$\text{Number of cells}/\mu\text{l} = (\text{average number of cells per field}) \times (\text{objective power})^2$$

The objective used to estimate leukocyte numbers should be that through which approximately 5–10 leukocytes are seen per field. For example, if an average of 5 cells were counted for each 50× field, the total leukocyte count would be (5) × (2,500) = 12,500 cells/μl.

ERYTHROCYTE EVALUATION Erythrocyte evaluation begins with the search for agglutination or rouleaux formation using a scanning objective. Erythrocyte morphology should be evaluated using the 100X, oil immersion lens in an area of the smear where red cells are evenly spaced, usually slightly behind the feathered edge. Red blood cells are evaluated for changes in size, shape, color, and inclusions. Erythrocytes are normally very uniform in size. Typically, minimal variation is found in the size, shape, or color of the erythrocytes in the blood smear of a normal cat or dog.

Nucleated red blood cells (NRBCs) are usually seen in regenerative anemias; however, they are not used to evaluate a regenerative response. A nucleated red blood cell in the absence of polychromasia is a dysplastic change and indicates a nonregenerative response. This may be observed in such conditions as lead poisoning, bone marrow damage due to septicemia, or myeloproliferative diseases (particularly erythroleukemia due to FeLV). When the number of nucleated erythrocytes exceeds 5–7/100 white blood cells (WBCs), the leukocyte count must be corrected for these cells. The formula for this correction is

$$\text{Corrected WBC} = (100 \times \text{WBCs}) / (100 + \text{number of NRBCs})$$

The interested reader is directed to a hematology text for the interpretation and significance of other erythrocytic abnormalities.

PLATELET EVALUATION Platelet evaluation begins with the search for clumps using a scanning objective. An estimation of platelet numbers is done using the 100× oil emersion lens. The formulas for estimation of platelet numbers are

Dog: Number of cells/μl = (number of cells per 100× oil field) × 15,000

Cat: Number of cells/μl = (number of cells per 100× oil field) × 20,000

The technique of platelet evaluation is particularly useful in evaluating platelets in the cat, since automated cell counts are often unreliable in assessing platelet numbers for this species. Megaplatelets, platelets as large or larger than erythrocytes, may indicate platelet regeneration due to a peripheral destruction or consumption of platelets. Thrombocytopenia may result form a production problem in the marrow or a loss in the peripheral circulation due to destruction or consumption of platelets. A bone marrow evaluation may be necessary to make this distinction.

LEUKOCYTE EVALUATION Leukocyte evaluation begins using a scanning objective by observing the mature neutrophil as the predominant cell type and identifying the presence of immature neutrophils (bands) or reactive changes in monocytes and lymphocytes. Large, immature blast cells should also be identified at this time.

These pathological changes and other changes then are evaluated more closely using the 100×, oil immersion lens. One important change in neutrophils is the presence of cytoplasmic toxicity. It is particularly important to evaluate toxicity of neutrophils in patients with a leukocytosis or a left shift. Toxicity is a cytoplasmic change usually associated with the presence of bacterial infections or toxins. A +1 toxicity is defined by the presence of Döhle bodies: small, basophilic aggregates of RNA in the cytoplasm of cells. This condition may be normal, if they are seen in low numbers of neutrophils in cats. A +2 toxicity shows Döhle bodies and diffuse cytoplasmic basophilia. A +3 toxicity contains all of the preceding plus foamy cytoplasmic vacuolation; and a +4 toxicity has all the preceding plus giantism and nuclear lysis. Hypersegmentation, although not a toxic change, is another significant finding in the neutrophil population. This is defined as the presence of a neutrophil with five or more lobes in the nucleus. Hypersegmentation is most commonly associated with steroid administration but may also be seen in myeloproliferative diseases or blood smears made from blood left too long in the vacutainer tube. Lymphocytes do not develop toxicity but may become reactive as a result of some antigenic stimulation from an infectious agent, neoplasm, or immune-mediated disease. The cytoplasm of reactive lymphocytes becomes more intensely basophilic, almost a royal blue. Reactive monocytes may also be seen if the cytoplasm becomes more intensely basophilic and vacuolated. This

usually indicates a chronic inflammatory process or may be seen with hemobartonellosis in the cat.

NEOPLASTIC CELLS IN CIRCULATION Neoplastic cells, primarily those of hematopoietic origin, may also be identified in the peripheral blood. These cells would alert the clinician to the possibility of a leukemia; however, this diagnosis technically must be made using a bone marrow aspirate. Hematopoietic blast cells may be of erythroid, granulocyte, monocyte, or rarely megakaryocyte origin (myeloproliferative disease), or lymphoid origin (lymphoproliferative disease). In general, they are identified as large cells with nuclei often two or more times the size of erythrocytes. They may have an abnormal nuclear morphology, including a high N:C ratio; a diffuse, altered chromatin pattern; and prominent nucleoli. The cytoplasm of these cells is often deeply basophilic.

Bone Marrow Evaluation

The evaluation of bone marrow is an important tool in the diagnosis of hematologic disorders and the staging of certain neoplasms. Proper sample collection and slide preparation may provide the basic information needed to assist in patient diagnosis or prognosis.

Indications

In most cases, indications for doing a bone marrow aspirate are determined by evaluation of a complete blood

count (CBC) on the peripheral blood. In fact, it is often impossible to interpret findings in the marrow without a recent CBC. The following is a list of indications for evaluation of a bone marrow aspirate.

ANEMIA Bone marrow aspirates should be performed whenever there is a nonregenerative or poorly regenerative anemia. It is not necessary to evaluate the bone marrow in cases of regenerative anemia, since the marrow is showing evidence of adequate red cell production.

LEUKOPENIA Reduced leukocyte numbers may result from lymphopenia or neutropenia. Lymphopenia is usually not an indication of decreased marrow production and does not typically require marrow evaluation. Neutropenia, on the other hand, may result from decreased production from the marrow or increased use or destruction in the periphery. A persistent neutropenia is a good indication for bone marrow evaluation.

THROMBOCYTOPENIA A bone marrow aspirate is important in differentiating a production problem verses peripheral destruction or utilization of platelets in patients with a peripheral thrombocytopenia.

UNEXPLAINED ELEVATION IN CELL NUMBERS Persistent polycythemia, leukocytosis, or thrombocytosis with no evidence of a clinical disease that could account for these findings is an indication for bone marrow evaluation.

ABNORMAL CIRCULATING CELLS The presence of abnormal cells in the peripheral blood may be an indication of neoplasia in the bone marrow and is an important indication for marrow evaluation. These may be in the form of hematopoietic blast cells, such as lymphoblasts or myeloblasts, or dysplastic cells. *Dysplasia* is defined as an abnormal maturation of cells, usually associated with a preleukemia or leukemia. Some examples of dysplastic changes are nucleated red blood cells with no evidence of polychromasia, abnormally large metarubricytes, hypersegmented neutrophils, giant metamyelocytes, megaplatelets, and dwarf megakaryocytes. Other clinical conditions may cause dysplastic changes in circulating cells in addition to leukemia or preleukemia. Lead poisoning may cause circulating NRBCs without polychromasia, and steroid administration is the most common cause of hypersegmentation of neutrophils. Additionally, the presence of nonhematopoietic cells in the peripheral circulation may be an indication for bone marrow evaluation. The presence of cells not normally found in circulation may suggest metastasis of a neoplasm to the marrow. The classic, and probably most common, example is the presence of mast cells in the blood of an animal with a mast cell tumor.

CLINICAL STAGING OF MALIGNANCY The absence of circulating neoplastic cells does not ensure the bone marrow is free of metastatic disease. This is particularly true of animals with lymphoma. Therefore, a marrow

evaluation is necessary for clinical staging and prognosticating.

UNEXPLAINED HYPERCALCEMIA In the dog, hypercalcemia is most often the result of a paraneoplastic syndrome associated with a lymphoid neoplasia or an anal sac apocrine gland adenocarcinoma. In cases of hypercalcemia with no lymph node or anal sac involvement, a bone marrow evaluation is of paramount importance. The majority of these animals have a lymphoid leukemia where only the bone marrow is involved. Circulating tumor cells may not be found in the peripheral blood.

MONOCLONAL GAMMOPATHY Monoclonal gammopathy is due to an increased production of a single immunoglobulin. This usually results from uncontrolled growth of a clonal population of B-lymphocytes. In small animals, monoclonal gammopathy is most often associated with lymphoproliferative disorders. Immunoglobulin-producing tumors include multiple myeloma, chronic lymphocytic leukemia, primary macroglobulinemia (Waldenström's syndrome), and lymphoma. A bone marrow aspirate is often needed to identify the neoplastic lymphocyte population.

Materials Needed

Bone marrow aspirates are performed using a sterile, 15- to 18-gauge Illinois sternal/iliac bone marrow aspiration

needle (Pharmaseal Division of Baxter Healthcare Corp., Valencia, CA). For core biopsies, a Jamshidi biopsy needle (11 gauge, 4 inches) should be used. Prior to aspiration of a sample, approximately 0.2 cc of anticoagulant (5% EDTA or heparin sulfate) is aspirated into a sterile 12-cc syringe. A 2% lidocaine solution is needed for local anesthetic to the periosteum in patients not undergoing general anesthetic. The marrow is deposited in a petri dish or other clear glass surface to allow the peripheral blood contamination to be tilted away from the marrow particles aspirated. The marrow particles adhere to the surface of the petri dish, where they can be removed by capillary action with a hematocrit capillary tube and transferred to microscope slides for smearing. Diff Quik or another, comparable stain can be used to fix and stain the air-dried smears.

Sample Collection

The hair is clipped and the bone marrow aspiration site is prepared with a surgical scrub. Preferred sites and patient positioning include dorsocranial or lateral aspects of iliac crest (patient is sternal), greater trochanter of the femur (patient is in lateral recumbency), and greater tubercle of the proximal aspect of the head of the humerus (patient is in lateral recumbency).

Using a 25-gauge needle, approximately 2–3 ml local anesthetic agent, lidocaine, is injected in and around the site where the bone marrow needle is to be introduced.

Care is taken to deposit lidocaine in and around all the tissues that extend from the skin to the bone.

The biopsy area is scrubbed a final time after the lidocaine is injected. A surgical drape may be applied for sterility.

The bone marrow site is identified, the skin is stretched between the thumb and index finger, and a small stab incision is made with a number 11 surgical blade in the area blocked with lidocaine. The bone marrow needle with the stylette in place is advanced through the stab incision in the skin, subcutaneous tissue, and muscle down to the bone. It is crucial to keep the stylette in place because it has a tendency to back out during the procedure. A 1- to 1.5-inch long, 16-gauge Illinois or Rosenthal bone marrow needle is preferred for dogs, and a 1-inch long, 18-gauge Illinois or Rosenthal needle is preferred for the cat. After a sample is obtained for cytologic evaluation, if a biopsy is required, a Jamshidi needle is utilized.

With the stylette in place, the bone marrow needle is advanced into the bone using a corkscrew motion. The instrument should not be allowed to wobble but should be fixed firmly into bone like a nail that has been securely hammered into wood. When the needle is firmly fixed in the bone, the stylette is removed and the syringe is affixed. Many clinical pathologists suggest rinsing the syringe and bone marrow needle with EDTA before the procedure to reduce clotting of the bone

marrow sample. The bone marrow sample then is aspirated briskly into the 12-ml syringe; usually, 1 ml is adequate. The aspiration may be accompanied with a few seconds of pain, but this cannot be prevented. If a sample is not obtained, the stylette is replaced in the bone marrow needle and the instrument is advanced farther into the bone for a second attempt at aspirating marrow contents.

Once marrow has been obtained, smears are prepared. The particle is blown onto one edge of a clean microscope slide and a second slide is laid parallel atop the first. The weight of the slide causes the material to diffuse out, leaving the particle in the center. The slides are gently slid apart making an even smear with marrow particles in the center of the slide. The slides are then stained with Diff Quik or a comparable stain.

Bone Marrow Evaluation

Valuable information can be obtained from marrow evaluation without advanced clinical pathology training. Interpretation of the bone marrow depends critically on the findings of a concurrent CBC. For example, if an animal has a high M:E ratio (more myeloid cells than erythroid), the CBC results may determine if it is due to an erythroid hypoplasia or a myeloid hyperplasia. The interpretation depends on whether the animal has a peripheral anemia or a leukocytosis.

CELLULARITY The cellularity of the marrow is determined by examining the relative amounts of fat and cellular material present in the marrow particles. Normal cellularity has approximately 50% cells and 50% fat; slightly more in young growing animals, and slightly less in geriatric patients. Increased cellularity or hyperplastic marrow (>75% cells) is seen in marrows responding to peripheral cytopenias (e.g., regenerative anemia, leukopenia, or thrombocytopenia). This also is noted in animals with an increased demand for leukocyte production (e.g., leukocytosis). Increased cellularity is also seen when the marrow is occupied by neoplastic cells (myelophthisic disease). Decreased cellularity (hypoplastic or aplastic marrow; >75% fat) is observed following insult or injury to one or more of the hematopoietic cell lines. This may result in an aplastic anemia, where all cell lines are decreased, or a cytopenia of only one or two of the different cell lines. Many infectious agents, drugs, hazardous materials, and immune-mediated diseases can cause hypoplastic or aplastic marrows. Unless previous exposure to drugs or infectious agents can be identified, most etiologies are undetermined and the disease is classified as idiopathic.

MARROW IRON OR HEMOSIDERIN The bone marrow is a major site for storage iron to be used in hemoglobin synthesis. Iron or hemosiderin appears as blue or black inclusions of amorphous material either in the background of

the smear or within the cytoplasm of marrow macrophages. The presence or absence of stainable iron must be evaluated within a unit particle. The evaluation of iron content in a marrow is significant only in anemic animals. The evaluation of iron stores in the marrow of dogs is a judgment call. If abundant stainable iron is seen within a unit particle, it is assumed to be increased. In the cat, stainable iron is normally not detected, so any amount of visible iron would be an indication of increased iron stores. Marrow iron stores are increased in the anemia of chronic inflammatory disease, hemolytic anemias, and in cases of decreased red cell production, such as red cell aplasia or aplastic anemias. Marrow iron stores are also increased in animals that have received recent blood transfusions. Decreased storage iron is seen in cases of iron deficiency. In small animals, this is associated almost exclusively with chronic blood loss. It should be noted that the absence of stainable iron in the marrow of cats cannot be used as an indication of iron deficiency, since stainable iron is not usually present in normal cats.

MEGAKARYOCYTES Megakaryocytes are the largest cells in the bone marrow, easily recognized with the 10× or 20× objective. Mature megakaryocytes have abundant amounts of pale blue cytoplasm that often contains fine eosinophilic granules. The cells appear to be multinucleated but actually contain a single, large, lobulated

nucleus. Immature megakaryocytes are smaller cells but are still at least two times larger than other hematopoietic precursors. They contain scant, deep blue cytoplasm and a round to slightly lobulated nucleus (four lobes or less). In normal marrow, the majority of the megakaryocytes should be mature. Increased numbers of immature cells are seen in a regenerative response to peripheral thrombocytopenias. One of the most common and most useful reasons for a veterinarian to evaluate a bone marrow is to assess a patient with a peripheral thrombocytopenia. Megakaryocyte numbers in the marrow allow classification of the disease as a production or a destruction problem. In a normal animal, one to three megakaryocytes should be seen while examining the marrow particles on a low power objective (10×). If the patient is responding to peripheral destruction or consumption of platelets, increased numbers of megakaryocytes are seen (megakaryocytic hyperplasia), some of which are immature. This patient has a much better prognosis and is more likely to respond to appropriate therapy than one with a production problem, where few to no megakaryocytes are found (megakaryocytic hypoplasia).

ERYTHROID SERIES Erythroid precursors are characterized by a round nucleus with dark, dense chromatin. The immature erythroid precursors (rubriblasts) are large cells with deep blue cytoplasm. They have a round

nucleus with clumped chromatin and one or more nucleoli. As these cells mature into rubricytes and metarubricytes, they become smaller, the nucleus becomes dark and pyknotic, and the cytoplasm changes from deep blue to gray. In normal marrow, the majority (>90%) of the erythroid precursors are mature cells, rubricytes, and metarubricytes. In normal marrow, the red cell series must mature all the way to anucleated, polychromatophilic erythrocytes (reticulocytes). If a bone marrow aspirate is performed to evaluate a peripheral anemia, we want to determine if we have an erythroid hyperplasia or erythroid hypoplasia. Erythroid hyperplasia has increased numbers of erythroid precursors (M:E ratio of <1), in the presence of a peripheral anemia. This indicates the bone marrow is responding to a peripheral loss or destruction of erythrocytes. Increased numbers of rubriblasts may be seen, but these cells should not exceed more than 10% of the total nucleated cell population. Phagocytosis of erythroid cells by marrow macrophages may indicate an immune-mediated destruction or be seen in patients who have had a recent blood transfusion. Erythroid hypoplasia, or decreased numbers of erythroid precursors (M:E ratio of >2) in the presence of peripheral anemia, indicates the bone marrow is not responding. This suggests the anemia is due to an erythrocyte production problem or an immune-mediated destruction of erythroid precursors.

MYELOID SERIES Immature myeloid cells (myeloblasts) have round to irregularly shaped nuclei with one or more nucleoli and paler cytoplasm than erythroid cells. The cytoplasm of these cells often contains fine eosinophilic granules (primary granules). The nuclei contain chromatin that is less clumped and more diffuse than the nuclei of the erythroid cells. In normal marrow, the majority (>90%) of the myeloid cells are myelocytes, metamyelocytes, bands, and segmented granulocytes. The neutrophil line is the most abundant cell type in the myeloid series. As the neutrophils mature to myelocytes, metamyelocytes, bands, and segmented neutrophils, the cytoplasm changes from light blue to clear, and the nucleus develops from bean shaped to banded to segmented. If the bone marrow is evaluated because of abnormal leukocyte numbers in the peripheral blood, we want to determine if there is a myeloid hyperplasia or a myeloid hypoplasia. Myeloid hyperplasia, or increased numbers of myeloid precursors (M:E ratio of >2), in the presence of a peripheral leukocytosis or leukopenia is most consistent with marrow responding to a peripheral demand for neutrophils. This may be seen in a number of immune-mediated and inflammatory diseases. Increased numbers of immature myeloid cells may be present; however, myeloblasts should not exceed more than 10% of the nucleated cell population, even in a strongly regenerative response. Myeloid hypoplasia, or decreased

numbers of myeloid precursors (M:E ratio of <1), in the presence of a peripheral leukocytosis or leukopenia, indicates decreased production of neutrophils by the marrow. This is particularly significant if the patient has a peripheral neutropenia. A number of chemotherapeutic agents, drugs, and infectious agents may damage the bone marrow, resulting in myeloid hypoplasia.

LEUKEMIAS Leukemia is a bone marrow neoplasm of the hematopoietic cells. Leukemia may be classified as a myeloproliferative disease (erythroid, myelogenous, or monocytic leukemia) or a lymphoproliferative disease (lymphoid leukemia), depending on the cell line from which the neoplastic population arises. Leukemia also is classified as acute or chronic, depending on the immaturity of the neoplastic cell. In all types of leukemia, the bone marrow is hypercellular. In acute leukemia, the neoplastic cell is the blast cell or immature precursor. Acute leukemia is diagnosed whenever the blast cell population of the marrow exceeds 30% of the nucleated hematopoietic cells. Acute leukemia may involve any one of the hematopoietic cell lines (erythroid, myelogenous, monocytoid, or lymphoid). Myeloproliferative diseases (erythroid, myelogenous, or monocytoid) may occasionally have two neoplastic cell lines occurring simultaneously (e.g., myelomonocytic). In cases of acute leukemia, it may be difficult to determine which type of leukemia is present without the use of special cytochemical stains.

Therefore, whenever acute leukemia is diagnosed, extra marrow slides should be air dried and mailed to a reference laboratory for classification. It is important to recognize that not all leukemia patients have blast cells in peripheral circulation. Some patients may have "aleukemic" leukemia. In chronic leukemia, the neoplastic cell is the mature blood cell (erythrocyte, granulocyte, lymphocyte, monocyte, or platelet). Patients with chronic leukemia have an unexplained, marked elevation of the affected cell line in the peripheral blood. With the exception of the chronic lymphocytic leukemia, the diagnosis is sometimes difficult because the neoplastic cells are mature and blast cells do not exceed 30% of the bone marrow population. Finding dysplastic changes in the hematopoietic cells in the peripheral blood or bone marrow may aid diagnosis (see the previous discussion of dysplastic changes). Patients with chronic leukemia have a better short-term prognosis than those with acute leukemia. In general, patients with lymphoid leukemia have a better prognosis with regard to survival time and response to therapy than patients with the comparable myeloproliferative disorder (e.g., acute lymphocytic leukemia vs. acute myelogenous leukemia). In lymphoid leukemia, hematopoietic cell lines other than lymphoid are not involved in the neoplastic process. Therefore, severe peripheral cytopenias are not usually encountered except in advanced cases, where myelophthisic disease has occurred.

Biopsy Guidelines

When Should You Obtain a Biopsy?

A preoperative biopsy should be obtained if it will change your choice of therapeutic modality or alter the degree or extent of therapy you choose. For example, it is very important to know the tumor type prior to surgery of the appendicular skeleton. Soft tissue sarcomas are locally invasive, aggressive tumors that usually require radical margin resection, whereas lipomas are benign and require only marginal resection. Pretreatment biopsies are also important if the knowledge that a pet has cancer will change the owner's willingness to treat the pet. Some owners are more willing to have their pet undergo a radical surgery, such as an amputation, if they know that there would be a good chance for cure, such as in the case of a fibrosarcoma.

Some masses, due to their location within a body cavity, are difficult to biopsy preoperatively. For example, obtaining a representative sample of a splenic or a solitary lung mass usually requires an exploratory laparotomy or thoracotomy, respectively. In these particular examples, the surgical removal of the mass is both diagnostic and therapeutic. The surgical treatment in both these examples would not have changed, even if the tumor type had been known prior to surgery.

Delaying obtaining a biopsy specimen until excision is also a possibility if retreatment is an option. For

example, if a small skin mass on the trunk is excised with dirty margins, plenty of tissue is left for a second operation without jeopardizing a cure with surgery. However, this would not necessarily be the same case with the same mass on the appendicular skeleton, where tissue for skin closure is at a premium.

Tumors are not homogeneous tissue masses. They contain areas of inflammation, necrosis, and reactive tissue. In general, the larger are the tissue samples, the better the diagnostic yield. Care should be taken not to create an excessive crush artifact with the surgical instruments when handling the biopsy sample. Cautery should be avoided on the biopsy specimen, as it alters the tissue architecture and cellular morphology. Adherence to aseptic technique reduces the chance of wound infection; however, all biopsy sites should be monitored closely for signs of infection and inflammation. Delayed healing at a tumor site may indicate wound infection or tumor regrowth.

Cancer and coagulation abnormalities often go hand in hand. Thrombocytopenia, disseminated intravascular coagulation, and increased heparin production are the most common coagulation abnormalities seen with cancer. A coagulation panel and buccal mucosal bleeding time should be evaluated in all suspect cancer patients prior to an invasive biopsy procedure.

Good preoperative biopsy technique allows for excision and radiation of all biopsy tracts during definitive

therapy. Gentle manipulation of the mass and the use of small gauge needles for aspiration minimize tumor seeding. Despite a short-lived increase in cancer cells documented within the efferent vessels and lymphatics on tumor manipulation, there is no real risk of distant tumor metastasis. When performing a surgical biopsy, blunt dissection of the surrounding soft tissues should be minimized and accurate hemostasis should be employed to prevent unnecessary local tumor seeding within the wound. In addition, biopsy sites should never be drained.

Biopsy Needles

CUTTING NEEDLES Various biopsy needles can be used for percutaneous biopsy. In general, newer automated needles are preferred. These spring-loaded needles are similar in style to manual Tru-cut needles. Automated needles can be completely automatic or semiautomatic. Completely automatic needles thrust the inner obturator (containing the biopsy tray or specimen notch) followed by the outer cutting sheath into the organ in a fraction of a second. These needles can easily be operated with one hand. Since the action is so quick, there is minimal displacement of the organ, a shorter intraparenchymal phase, and much more reliable yield of tissue. This allows the organ to be biopsied with minimal manual mobilization and allows use of a smaller diameter needle and a lighter degree of sedation. In addition,

extremely soft tissues (such as lung) tend to be less fragmented by the rapid cutting action.

SEMIAUTOMATIC NEEDLES Semiautomatic needles require manual thrusting of the internal obturator (containing the biopsy tray or specimen notch) into the organ, followed by an automatic thrusting of the outer cutting sheath by the spring-loaded mechanism. These needles have some of the advantages of the completely automatic needles and the additional advantages of more control over the final needle position, lighter weight with a smaller handle, and precise localization of the needle tip before the outer cutting sheath is "fired." The older, manual cutting needles offer no advantages over these newer needles.

ASPIRATION NEEDLES Aspiration needles are generally used to obtain smaller samples that would be suitable for cytologic preparations (rather than histopathology). These needles are also well suited to obtain samples of fluid, such as intraparenchymal cysts, loculated effusions, gall bladder puncture, etc. Usually these are smaller gauge needles (20–22 gauge) and therefore tend to be less traumatic.

Biopsy Methods

PUNCH BIOPSY Biopsy punches are disposable and available in diameters ranging from 2 to 6 mm. Generally,

larger biopsies are preferred so the pathologist has adequate tissue to make a histologic diagnosis. When possible, the junction between normal and abnormal tissue should be biopsied. Punch biopsies are usually inadequate to obtain tissue below the dermis; subcutaneous fat is rarely obtained in the average punch biopsy of the skin.

The hair is clipped and the surgery site prepared with a surgical scrub. Using a 25-gauge needle, approximately 2–3 ml of the local anesthetic agent lidocaine is injected around the lesion. It is important to not distort or disturb, with lidocaine, the normal architecture of the tissue to be biopsied. The biopsy area is scrubbed a final time after the lidocaine is injected. The skin is stretched between the thumb and index finger. The biopsy punch is placed at right angles to the skin surface. The punch is rotated in one direction while at the same time firm downward pressure is applied until the subcutis is reached. The punch is then angled almost parallel with the skin while still applying pressure along the long axis of the biopsy punch. The punch is rotated to sever the base of the biopsied material. The punch is removed. The core of tissue is gently elevated with the point of a needle and the base severed with a scalpel or iris scissors. One or two sutures are placed to close the defect.

INCISIONAL BIOPSY In some cases, an incisional biopsy is preferred over a punch biopsy because larger sections of tissue can be obtained for histologic diagnosis. In

addition, if the lesion is biopsied at the junction of the normal and abnormal tissue, a "wedge" of tissue is obtained that retains a larger section of the tissue's architecture. This allows the histopathologist to better see characteristics of malignancy, such as invasion of normal tissue.

The animal is placed under general anesthesia after routine screening tests have been performed to identify problems such as coagulopathies and metabolic disease. The hair is clipped and the surgery site prepared with a surgical scrub. After the region is draped, an elliptical or wedge incision is made at the margin of the normal and abnormal tissue. Care is taken to obtain adequate tissue and ensure that a subsequent definitive surgery can successfully remove the tumor and the incisional biopsy incision. Vessels going to and from the tissue to be biopsied are carefully identified and ligated. The specimen is lifted and severed at the base with either a scissors or a scalpel blade. The incision is sutured for closure.

EXCISIONAL BIOPSY An excisional biopsy should be performed when tissue is required for a histologic diagnosis, but the lesion must be small enough and in an anatomic location that allows wide surgical removal without compromising the normal tissue around it. In general, an excisional biopsy is preceded with, at least, fine-needle aspirate cytology to give the surgeon as much information as possible about the characteristics of the tumor prior to removal. For example, a mast cell tumor or a soft

tissue sarcoma requires wide surgical margins (2–3 cm), whereas a sebaceous cyst or sebaceous adenoma could be treated with smaller margins.

This biopsy is performed in the same manner as an incisional biopsy except the lesion is excised completely, with adequate margins.

NEEDLE CORE BIOPSY Needle core biopsy is generally safe and quick and can be performed on an awake, cooperative patient. The histopathologic results are generally more accurate than fine-needle aspirate cytology but not as accurate as excisional biopsy.

The lymph node is grasped by an assistant and held firmly against the overlying skin, and the biopsy site is prepared as noted earlier. Approximately 2–3 ml 2% lidocaine is injected under the skin overlying the enlarged lymph node. Using a number 11 surgical blade, a stab incision is made in the skin to allow ease of entry of the needle core biopsy instrument. The needle core biopsy instrument is advanced through the incision and into the capsule of the enlarged lymph node for subsequent biopsy. At least three to five biopsies are taken of the lymph node through the same stab incision. The needle biopsy specimens are fixed in 10% buffered formalin as described already. A separate container should be used for each lesion biopsied. The stab incision is sutured only if indicated.

LYMPH NODE BIOPSY Lymph node biopsy is often important in the diagnosis, staging, and proper therapeutic management of the pet with cancer. A biopsy is often performed after fine-needle aspirate cytology suggests the presence of a disease. Despite the accuracy of fine-needle aspirate cytology in determining certain diseases such as lymphoma, mast cell tumors, and the presence of metastatic solid tumors, a histopathologic diagnosis is always recommended prior to initiation of therapy. In each case, adequate tissue must be obtained for histopathologic diagnosis and special stains, if indicated. When possible, the submandibular lymph nodes should be avoided; they often are reactive in the normal animal because they drain the oral cavity, where the bacterial count is usually quite high. These reactive cells are sometimes misdiagnosed as neoplastic cells. If a carcinoma or a sarcoma is suspected, a biopsy should not be performed unless an overall plan for definitive therapy is made because the biopsy procedure can "seed" the operative field with tumor cells if the principle of en bloc dissection is violated. As with all biopsies, the surgeon who will perform the definitive surgery should be consulted prior to the biopsy to ensure that incisions are properly placed for a subsequent definitive procedure.

Biopsy Specimen Handling Considerations

Punch biopsy specimens should be removed from the forceps with the utmost of care. These minute specimens

are readily subject to crush and squeeze artifact, particularly before fixation. Specimens should be teased from the forceps with a needle and gently placed on lens paper or specially designed biopsy sponges presoaked in formalin. Attempts to reorient specimens on the surfaces should be avoided. After all specimens are placed on a suitable surface, the biopsies are immersed in formalin and submitted to the laboratory. Fixation in 10% neutral buffered formalin is adequate for routine histologic examination. Glutaraldehyde fixation is optimal for specimens for electron microscopic examination. Fresh frozen tissue (e.g., via liquid nitrogen) may be required for immunohistochemical studies of certain antigens.

Diagnostic Imaging

As in human medicine, veterinary medicine has shown an increasing trend toward noninvasive procedures to diagnose many different types of the neoplasia, whether primary or metastatic. In response to this need and technologic advances, radiology has evolved to include many different forms of imaging in nuclear medicine, color flow and power doppler ultrasonography, and magnetic resonance imaging (MRI).

Plain Film Survey Radiography

Despite new advances, plain film radiographs remain the standard. The radiograph is not intended to serve as a

shortcut diagnosis or take precedence over a thorough physical examination. It provides information about disease location, type, and extent; supplements findings from the database; and helps formulate and integrate treatment strategies. Radiographic interpretation must be consistent and thorough. Procedurally, the clinician should assess the radiographic technical quality, check for artifacts, evaluate extrathoracic structures (spine, ribs, soft tissue), analyze thoracic organs and structures (trachea, heart, lungs), assess breed-specific anatomic variations, and correlate areas of concern or suspicion with the database, including physical examination, ECG, clinical pathology, echocardiogram, and other imaging techniques.

Nuclear Medicine

Nuclear medicine techniques have been used extensively in humans to diagnose various forms of cancer. In fact, nuclear oncology is one of the most promising fields, as new, tumor-specific radiopharmaceuticals are introduced with increasing frequency. Veterinary nuclear medicine is being used clinically to help diagnose the presence of primary bony and soft tissue tumors as well as in the staging of potential metastatic disease. The thyroid scan using either ^{99}m TcO_4 or ^{123}I have been used to evaluate suspect thyroid adenocarcinomas in both dogs and cats. Although a thyroid scan cannot differentiate benign versus malignant disease, it is helpful as a screening tool.

Benign hyperfunctional thyroid glands have round or oval shapes and homogeneous uptake with intense centers and tapering margins. "Hot nodules" or dumbbell-shaped glands are common, as is benign ectopic thyroid tissue. Glands that have irregular shapes and heterogeneous uptake with multiple photopenic areas and evidence of extension (invasion) into adjacent fascial planes are suggestive of a malignant tumor. Thyroid scans can also be useful in diagnosing distant metastatic disease to the lungs or bone. Thyroid scans have proven to be useful in predicting the ease of which a tumor can be surgically removed or debulked, by providing an estimate of peritumoral invasion.

Bone scans are used with increasing frequency to evaluate possible bony metastatic disease. Although the frequency of skeletal metastasis from primary bone tumor is low, the presence of metastatic disease may greatly alter the treatment plan or the owner's decision to treat at all. The incidence of metastatic disease to bone from other types of tumors has not been evaluated extensively. It is known, however, that prostatic and mammary gland adenocarcinomas, as well as transitional cell carcinomas, may metastasize to the bone. Bone scanning is the most sensitive and economical way to evaluate this possibility.

Gallium (67 Ga) has been used in humans to detect local recurrences of primary soft tissue sarcomas as well as define the presence of regional metastasis. Tumor types evaluated in humans include leiomyosarcomas,

mesotheliomas, schwannoma, rhabdomyosarcoma, fibrosarcoma, liposarcoma, and synovial cell sarcoma. The 67 Ga appears to be specific for active malignant sarcomatous tissue and can differentiate benign fibrous (scar) tissue from active tumor tissue. In this regard, 67 Ga appears to diagnose primary soft tissue fibrosarcomas and demonstrate regional metastatic "skip" lesions, guiding the surgeon for more complete surgical removal as well as diagnose early recurrence. The uptake in these tumors does not appear altered by previous radiation, chemotherapy, or soft tissue surgery. All sarcomatous tissue seen had marked, heterogeneous uptake and mostly poorly defined margins.

Ultrasonography

Ultrasound is used extensively to evaluate intra-abdominal, intracardiac and heart base neoplasia. Similar to many forms of nuclear scintigraphy, ultrasound is very sensitive but in many cases rather nonspecific. Ultrasound is especially sensitive when there is nodular or multinodular disease, where the nodules have different acoustic properties than the surrounding tissue parenchyma. It is much less sensitive in diagnosing diffuse diseases, such as mast cell tumors or lymphosarcoma. Ultrasound-guided aspirates and Tru-cut biopsies have become the method of choice for obtaining tissue samples for cytologic or histologic diagnosis. The advantages of ultrasound-guided tissue sampling are many and

include minimal morbidity, the ability to sample specific nodules and normal tissue, and the ability to sample nodules located deep within an organ. The disadvantages include limited tissue sample volume.

Color flow doppler ultrasound has been investigated in many types of tumors to evaluate increased blood flow and abnormal arteriovenous shunting. Recently, an alternative to the display of frequency information with color flow doppler imaging is to use a color map that displays the integrated power of the doppler signal instead of its mean frequency shift. The result is an absence of aliasing. The image gives no information regarding the direction of flow or velocity and is much less angle dependent than frequency-based color flow imaging, where noise from vessel wall movements may add to the displayed information. This form of doppler is referred to as *power doppler*. The resultant image permits higher effective gain settings for flow detection and increased sensitivity for flow detection and is especially useful for evaluating slow flow.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is commonly used to diagnose many forms of neoplasia that, due to location, are difficult to evaluate using other modalities. Examples include brain and brain stem neoplasia, spinal cord tumors, and adrenal tumors. MRI has proven helpful in demonstrating the size, shape, and amount of local tis-

sue invasion. For nasal adenocarcinomas, it is much more sensitive than even high-quality radiographs in evaluating the extent of disease. It has been shown to be superior to computed tomography (CT) in determining invasion into the rostral brain. It is also felt to be superior to CT in differentiating tumor tissue versus trapped fluid in the frontal sinus. CT, on the other hand, is considered more sensitive than MRI in evaluating bony lysis secondary to tumor invasion. MRI cannot differentiate among types of primary brain neoplasia; but based on the tumor's location, amount of signal intensity on T1, T2, proton density, and contrast-enhanced T1 images, an educated guess can often be made.

3

Tumor Tidbits

Acute Lymphoid Leukemias in Dogs and Cats

Common Clinical Signs:	Rapid onset of anorexia and weight loss; lymphadenopathy is common.
Common Histologic Types:	Lymphocytosis >20,000 cells/µl whole blood; predominantly lymphoblasts; difficult to differentiate from lymphoma.
Biological Behavior:	May occur at any age; large breed dogs or young cats; most cats are FeLV antigenemic.
Prognostic Findings:	None identified.

Treatment Considerations:	Supportive treatment—antibiotics and transfusions of blood and blood products. Chemotherapy—consider using prednisone and Elspar to initially decrease malignant cell counts, then follow using a combination drug protocol (see protocols 6 and 7; protocols are outlined in Chapter 7) and anticipate a 60–70% remission rate for a median duration of 7–9 months.

Acute Nonlymphoid Leukemia in Dogs and Cats

Common Clinical Signs:	Nonspecific; rapid onset of inappetence and lethargy; clinical signs reflect cytopenias; hepatosplenomegaly.
Common Histologic Types:	Not clinically relevant to distinguish because of poor prognosis, but terminology includes acute myeloid (granulocytic), myelocytic, promyelocytic, monocytic, monoblastic, myelomonocytic, megakaryocytic, and erythroleukemic;

	myelomonocytic is the most common type.
Biological Behavior:	May occur at any age; female dogs or young cats; FeLV antigenemia in 90% or more of cats; rapidly progressive; organ infiltration is common.
Prognostic Findings:	None identified.
Treatment Considerations:	Supportive treatment—antibiotics and transfusions of blood and blood products. Chemotherapy—no real efficacy of chemotherapy in this disease, aggressive chemotherapy often causes marrow ablation and death.

Anal Sac Adenocarcinoma

Common Clinical Signs:	Dyschezia, perianal mass, and polyuria and polydipsia due to hypercalcemia.
Common Histologic Types:	Adenocarcinoma.
Biological Behavior:	Old, female dogs; production of parathyroid hormone-related protein causes hypercalcemia; metastasis to regional lymph nodes is common.

Prognostic Findings:	Dogs with hypercalcemia or with detectable metastases have shorter survival times.
Treatment Considerations:	Surgery—may require local excision of tumor and sublumbar lymph nodes; surgery usually resolves hypercalcemia.
	Radiation therapy—applied to local tumor site and sublumbar nodes to prevent tumor regrowth; may resolve hypercalcemia.
	Chemotherapy—may be useful as an adjunct to surgery or radiation therapy; consider cisplatin, Adriamycin, or mitoxantrone (see protocols 1–4).

Bone Tumors in Cats

Common Clinical Signs:	Lameness for appendicular tumors (60% of tumors); palpable mass for axial tumors, which most commonly affect the head; primarily lytic lesions.
Common Histologic Types:	Osteosarcoma.
Biological Behavior:	Old cats; no obvious gender predilection; metastatic rate is low.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—potential for cure if surgery eliminates all tumor (e.g., amputation). Radiation therapy—seems to improve local control of osteosarcoma. Chemotherapy—not reported.

Brain Tumors in Cats

Common Clinical Signs:	Sudden-onset visual deficits and neurologic dysfunction.
Common Histologic Types:	Meningioma.
Biological Behavior:	Old cats (75% >9 years of age); locally invasive, rare metastases.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice due to slow regrowth of meningioma. Radiation therapy—may be useful adjunct to incomplete excision.

Brain Tumors in Dogs

Common Clinical Signs:	Seizures and temperament changes.

Common Histologic Types:	Meningioma.
Biological Behavior:	Mixed breeds and boxers; old dogs (10 years of age and older); slight male predilection; locally invasive, rare metastases.
Prognostic Findings:	Worse prognosis with severe neurologic dysfunction, abnormal cerebrospinal fluid, or multiple tumors.
Treatment Considerations:	Palliation—corticosteroids and anticonvulsants.
	Surgery—may be beneficial for meningiomas.
	Radiation therapy—treatment of choice for gliomas; useful alone or as an adjunct to surgery for meningiomas.
	Chemotherapy—hindered by blood-brain barrier; possible role for carmustine and lomustine.

Cardiac Hemangiosarcoma in Dogs

Common Clinical Signs:	Collapse and cardiac tamponade; hind limb paresis; and right atrial mass.

Common Histologic Types:	Hemangiosarcoma.
Biological Behavior:	Average age is 10 years; German shepherds are predisposed; metastasis may be widespread, common to lungs.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—palliative in dogs with resectable lesions. Chemotherapy—consider Adriamycin-based protocols (see protocol 1).

Chronic Lymphocytic Leukemia in Dogs

Common Clinical Signs:	Nonspecific; often asymptomatic.
Common Histologic Types:	Mature lymphocytosis; differentiate from reactive lymphocytosis and well-differentiated lymphoma.
Biological Behavior:	Old dogs; often slow to progress.
Prognostic Findings:	None identified.
Treatment Considerations:	Supportive treatment—repeated monitoring by blood counts may be all that is required for asymptomatic animals.

	Chemotherapy—combined use of prednisone and an alkylating agent (Cytoxan, melphalan, or Leukeran) provides long-term remissions in symptomatic dogs.

Cutaneous and Extramedullary Plasmacytomas in Dogs

Common Clinical Signs:	Solitary cutaneous mass in trunk or limbs; may affect oral cavity, ears, and head; less commonly, may occur in multiple or other sites, such as diffuse gastrointestinal (GI) tumors.
Common Histologic Types:	Mature plasma cells.
Biological Behavior:	Old dogs; cutaneous tumors are usually benign; plasmacytoma of other sites (e.g., GI) may metastasize.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—surgery with wide surgical margins is curative in most cases of cutaneous plasmacytoma. Radiation therapy—radiation-sensitive tumor.

	Chemotherapy—melphalan, prednisone, and doxorubicin have caused tumor responses, often for a long duration in dogs with extramedullary plasmacytoma.

Cutaneous Hemangiosarcoma in Dogs

Common Clinical Signs:	Raised, red lesion, often in skin that is lightly pigmented.
Common Histologic Types:	Hemangiosarcoma.
Biological Behavior:	Average age is 10 years; whippets and other dogs with glabrous skin are predisposed; metastasis is uncommon.
Prognostic Findings:	Histopathologic evidence of solar elastosis adjacent to tumor is good prognostic sign.
Treatment Considerations:	Surgery—curative for dermal origin tumors; approximately 30% of subcutaneous origin tumors metastasize.
	Radiation therapy—radiation-sensitive tumor; excellent local control for incompletely excised tumors.

	Chemotherapy—role undecided due to low metastatic rate and resultant lack of need for adjuvant therapy.

Cutaneous Melanoma in Dogs

Common Clinical Signs:	Darkly pigmented epidermal lesion, usually raised but not ulcerated.
Common Histologic Types:	Most are well differentiated (benign); subungual tumors are more aggressive.
Biological Behavior:	Adult to aged dogs.
Prognostic Findings:	Subungual melanoma, 50% metastasize; other cutaneous sites, metastasis is rare.
Treatment Considerations:	Surgery—surgical excision curative for most cutaneous lesions
	Radiation therapy—radiation-sensitive tumor; >85% local control rates observed for 2 years or longer.
	Chemotherapy—cisplatin or carboplatin chemotherapy for metastatic lesions or possibly as an

adjunct to surgery in subungual melanoma; see protocol 5.

Cutaneous Squamous Cell Carcinoma in Cats

Common Clinical Signs:	Ulcerated cutaneous lesions, most often on head and neck.
Common Histologic Types:	Most are well differentiated; metastasis to regional lymph nodes is rare.
Biological Behavior:	Cats lacking skin pigment are prone to actinically induced tumors; tumors are locally invasive with a low metastatic rate.
Prognostic Findings:	None identified.
Treatment Considerations:	Early lesions—brachytherapy, radiation therapy, local current-field hyperthermia, photodynamic therapy, and cryotherapy if lesions are <1 cm. Invasive lesions—external beam radiation therapy, surgery, photodynamic therapy, and intralesional chemotherapy may be considered. Chemotherapy—anecdotal reports of bleomycin have shown efficacy.

Cutaneous Squamous Cell Carcinoma in Dogs

Common Clinical Signs:	Ulcerated cutaneous lesions, most often on limbs (digits); lesions may be induced by sunlight on trunk.
Common Histologic Types:	Most cutaneous squamous cell carcinomas are well differentiated and rarely metastasize.
Biological Behavior:	Large, black-breed dogs are prone to subungual tumor, which may metastasize; light-skinned dogs are prone to actinically induced tumors.
Prognostic Findings:	Nasal-plane tumors more aggressive; subungual and skin tumors may metastasize; lymphatic invasion for subungual lesion does not influence prognosis for survival.
Treatment Considerations:	Early lesions—surgical excision, retinoids, topical 5-fluorouracil or carmustine ointments, and cryotherapy if lesions are <1 cm. Invasive lesions—surgery, with or without radiation therapy and intralesional chemotherapy.

	Metastatic lesions—cisplatin or mitoxantrone chemotherapy.

Erythrocytosis in Dogs and Cats

Common Clinical Signs:	Polyuria, polydipsia, bleeding, seizures, and hyperemic mucous membranes.
Common Histologic Types:	Mature erythrocytosis; rule out relative and secondary polycythemia.
Biological Behavior:	Middle-aged animals; no breed predilection; bleeding and seizures due to hyperviscosity; elevated red cell mass with no increase in erythropoietin.
Prognostic Findings:	None identified.
Treatment Considerations:	Phlebotomy—periodic removal eventually induces iron deficiency and microcytic cells that may assist in palliation. Chemotherapy—hydroxyurea has shown efficacy giving long remission durations.

Pancreatic Tumors (Exocrine) in Dogs

Common Clinical Signs:	Nonspecific anorexia and weight loss.
Common Histologic Types:	Exocrine pancreatic carcinoma.
Biological Behavior:	Old dogs (mean age is 9 years); cocker spaniels may be predisposed; high metastatic rate.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—may not be beneficial due to high metastatic rate. Chemotherapy—anecdotal reports of Gemzar efficacy in dogs.

Hemangiosarcoma in Cats

Common Clinical Signs:	Intraabdominal and cutaneous tumors occur with similar frequency as in dogs.
Common Histologic Types:	Hemangiosarcoma.
Biological Behavior:	Cutaneous hemangiosarcoma may be sunlight induced in areas of unpigmented skin.
Prognostic Findings:	Hemangiosarcomas of spleen and mesentery are highly metastatic;

	tumors of skin are highly recurrent and >50% develop metastasis.
Treatment Considerations:	Surgery—excision of cutaneous tumors is reported to be curative by some if margins are wide; survival <6 months reported by others regardless of surgical procedure.
	Radiation therapy—radiation-sensitive tumor; prognosis guarded due to metastatic behavior.
	Chemotherapy—unproven but consider protocol 7.

Hyperadrenocorticism in Dogs

Common Clinical Signs:	Hypercortisolism, polydipsia, polyuria, and cutaneous changes; nervous system dysfunction with large pituitary tumors.
Common Histologic Types:	Pituitary adenomas of par distalis in 80% of dogs; less commonly, adrenal gland tumors (usually carcinoma).
Biological Behavior:	Middle-aged to old dogs; poodles, dachshunds, and boxers are at higher risk; no gender predilection; metastasis is rare for pituitary

	tumors but common for adrenal tumors.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice for adrenal tumors.
	Medical management—for pituitary tumors, mitotane and ketoconazole offer good long-term palliation by their effects of adrenal cortical destruction and interference with steroid synthesis, respectively; L-deprenyl may also be a useful agent; mitotane (o,p'-DDD) may be a useful agent at high doses for adrenal tumors.
	Radiation therapy—provides good palliation for neurologic dysfunction caused by large pituitary tumors and gives moderate control of cortisol levels.

Hypereosinophilic Disease in Cats

Common Clinical Signs:	Gastrointestinal signs due to eosinophilic infiltration; often chronic history.

Common Histologic Types:	Mature eosinophilia; rule out allergic diseases and eosinophilic granuloma complex.
Biological Behavior:	Adult cats (median age is 8 years); females may be predisposed; cats may have widespread organ infiltration.
Prognostic Findings:	None identified.
Treatment Considerations:	Prednisone and hydroxyurea may be palliative, consider dietary modification using hypoallergenic diets.

Injection Site–Associated Sarcomas in Cats

Common Clinical Signs:	Mass near site of previous vaccination.
Common Histologic Types:	Fibrosarcoma or other soft tissue sarcoma; other histologic types have been reported (malignant fibrous histiocytoma).
Biological Behavior:	Tumor develops months to years after vaccination; multiple vaccinations at the same site at one time increase risk of tumor development; locally aggressive; frequent recurrence after surgery; rare distant metastasis.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice; wide and deep surgical margins are essential for all tumors. Radiation therapy—should be consider prior to surgical excision to reduce tumor burden and provide greater local control. Chemotherapy—unproven efficacy alone but should be considered concurrently with radiation therapy; consider Adriamycin or mitoxantrone (see protocols 4, 7, and 10).

Insulinoma in Dogs

Common Clinical Signs:	Hypoglycemia and hyperinsulinemia; tachycardia and neurologic signs may be intermittent; peripheral polyneuropathy may cause tetraparesis.
Common Histologic Types:	Carcinoma.
Biological Behavior:	Old dogs with no gender predisposition; large-breed dogs are more commonly affected; most tumors are highly metastatic.

Prognostic Findings:	Dogs with tumors confined to pancreas have a longer symptom-free period and survival after surgery; dogs that have only lymph node metastasis live longer than dogs with distant metastasis.
Treatment Considerations:	Surgery—treatment of choice for localized tumors.
	Medical management—prednisone, diazoxide, Sandostatin, octreotide, and propranolol may control hypoglycemia.
	Chemotherapy—streptozotocin and alloxan may be effective; however, both are extremely nephrotoxic and require diuresis.

Intestinal Tumors in Cats

Common Clinical Signs:	Small intestine—vomiting, weight loss, and anorexia.
	Large intestine—hematochezia.
Common Histologic Types:	Adenocarcinoma; other tumors are rare.
Biological Behavior:	Old cats; mean age is 11 years; Siamese are predisposed; tumors usually cause annular constriction;

	and metastasis to peritoneal surfaces is common.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—surgical resection results in 15-month average survival; some cats live more than 2 years; lymph node metastasis at surgery does not always influence survival.
	Chemotherapy—unproven effect on survival but consider protocol 10 as adjunctive to excision or protocol 7 if surgery cannot be performed.

Intestinal Tumors in Dogs

Common Clinical Signs:	Duodenum/jejunum—vomiting, melena.
	Jejunum/ileum—weight loss and diarrhea.
	Colon/rectum—tenemus and hematochezia.
Common Histologic Types:	Adenocarcinoma; less commonly, leiomyosarcoma and lymphoma; leiomyosarcoma common in the cecum.

Biological Behavior:	Old, male dogs; most tumors are adenocarcinoma; adenocarcinoma is more likely to metastasize than leiomyosarcoma, usually to regional lymph nodes.
Prognostic Findings:	Colorectal—dogs with annular lesions have poor chance of survival; other types of lesions have a better prognosis.
Treatment Considerations:	Surgery—little information for adenocarcinoma; average survival of dogs with colorectal adenocarcinoma is 15 months after surgery; median survival is >1 year for leiomyosarcoma.
	Radiation therapy—rectal adenocarcinoma may be controlled by high-dose fractions; median control is >6 months.
	Cryotherapy—small, minimally invasive tumors of the rectum and distal colon.
	Chemotherapy—consider adjunct to surgery or radiation therapy; consider protocol 1, 2, or 4.

Liver Tumors in Cats

Common Clinical Signs:	Nonspecific lethargy and anorexia; cats often have a palpable mass.
Common Histologic Types:	Intrahepatic bile duct tumors (more than half are benign); hepatocellular carcinoma is next most common type.
Biological Behavior:	Most cats >10 years of age; intrahepatic bile duct tumors may progress from benign to malignant; benign tumors usually involve a solitary lobe; carcinomas often metastasize.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice for benign tumors; however, carcinomas are usually diffuse and prognosis is poor. Chemotherapy—rarely considered due to hepatic insufficiency to metabolize anticancer agents.

Liver Tumors in Dogs

Common Clinical Signs:	Nonspecific lethargy and weight loss; dogs may be asymptomatic and may have a palpable mass.

Common Histologic Types:	Primary hepatocellular carcinoma.
Biological Behavior:	Old dogs; large solitary lesions have low metastatic rate, but the majority have multiple nodular or diffuse involvement.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice; dogs with solitary hepatocellular carcinoma, regardless of size, have a good prognosis after resection (median survival exceeds 1 year). Chemotherapy—palliative use of alkylating agents (Cytoxan and Leukeran) have been beneficial in dogs with diffuse or nodular disease.

Lower Urinary Tract Tumors in Cats

Common Clinical Signs:	Hematuria, mucoid vaginal discharge, and other signs of bladder inflammation.
Common Histologic Types:	Transitional cell carcinoma, squamous cell carcinoma.
Biological Behavior:	Old cats, except lymphoma and rhabdomyosarcoma.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—recurrence is common unless surgery is aggressive; cats are more amenable to surgery than dogs, because tumors are more cranioventral in location.
	Chemotherapy—may be helpful; consider protocol 4 for carcinomas and protocol 6 or 7 for lymphoma.

Lower Urinary Tract Tumors in Dogs

Common Clinical Signs:	Mimic infection—hematuria, stranguria, and pollackiuria; dogs often have secondary infections.
Common Histologic Types:	Transitional cell carcinoma.
Biological Behavior:	Old dogs, usually female; insecticidal dips and obesity may be associated with development of bladder tumors.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—palliative only; most tumors involve trigone region of the bladder.

Radiation therapy—excellent local control; however, fibrosis of bladder may occur as a late effect.

Chemotherapy—palliative at best, should be consider adjuvant to surgery or radiation; best results are seen with mitoxantrone combined with piroxicam (protocol 4) followed by carboplatin or piroxicam.

Lung Tumors in Dogs and Cats

Common Clinical Signs:	Persistent cough, dyspnea, hemoptysis, lameness in cats (metastasis to digits), hypertrophic osteopathy (in dogs), anorexia, lethargy, and malaise.
Common Histologic Types:	Adenocarcinoma (bronchogenic) is most common.
Biological Behavior:	Disease of older aged animals; tumors are likely to cause pleural effusion and respiratory stridor; metastases are common early in the course of the disease.
Prognostic Findings:	Normal appearing hilar regional lymph nodes are associated with significantly longer survival time

	following surgery than enlarged nodes; effusion, increasing size, and presence of metastases are also negative prognostic signs.
Treatment Considerations:	Surgery—lung lobectomy is the treatment of choice in dogs and cats without effusive disease; median survival exceeds 1 year.
	Chemotherapy—unproven results, consider protocols 1–3 or 10 adjuvant to surgery due to the high metastatic potential for lung tumors.

Lymphoma in Cats

Common Clinical Signs:	Anterior mediastinal or alimentary involvement.
Common Histologic Types:	Typically mixed B and T cell.
Biological Behavior:	Often FeLV positive but depends on anatomic location of lymphoma; occurs in all breeds with a bimodal age peak.
Prognostic Findings:	Single nodal (mediastinal) or extranodal (nasal) location stage better than multiple locations.

	FeLV positive—worse survival rate, no effect on response to therapy.
Treatment Considerations:	Surgery—considered only for localized conditions (intestinal).
	Radiation therapy—extremely radiation-sensitive tumor; consider for curative intent for nasal locations.
	Chemotherapy—consider protocols 6 and 7 as primary therapy or adjunct to surgery or radiation therapy; median survival typically ranges from 6–12 months (mediastinal) to >18 months (nasal or if radiation or surgery used).

Lymphoma in Dogs

Common Clinical Signs:	Generalized peripheral lymphadenopathy.
Common Histologic Types:	Diffuse large cell, immunoblastic, and small lymphocytic.
Biological Behavior:	All breeds, middle-aged, systemic disease.
Prognostic Findings:	Clinical stage—advancing stage and dogs with clinical signs are associated with a worse prognosis.

	Hypercalcemia—worse when associated with an anterior mediastinal mass.
	Sex—female dogs have a better prognosis than male dogs.
	Body size—small dogs do better than large dogs.
	Pretreatment corticosteroids: worse (controversial findings).
	High grade: higher response rate and longer duration of remission.
Treatment Considerations:	Surgery—rarely considered unless confined to a single node.
	Radiation therapy—unproven efficacy; considered in the palliative care of multidrug-resistant lymphoma (4–6 months additional remission).
	Chemotherapy, single agent—prednisone, cyclophosphamide, vincristine show 50% complete remission (CR) for a median of 1–6 months; doxorubicin shows 60–75% CR for a median of 6–8 months.
	Chemotherapy, combinations—various usages of multiple drugs show 70–80% CR for a median of

9–18 months (see protocols 6 and 7).

Mammary Tumors in Cats

Common Clinical Signs:	Presence of a mass in the mammary chain.
Common Histologic Types:	Mammary adenocarcinoma.
Biological Behavior:	Siamese may be at increased risk; most affected cats are 10–12 years of age; 70–90% of tumors are malignant; >25% are ulcerated; >50% involve multiple glands; >80% have metastases at time of euthanasia.
Prognostic Findings:	Increasing tumor size is associated with a poor prognosis.
Treatment Considerations:	Surgery—mastectomy of the affected side is superior to regional resection; recurrence is unlikely to be reduced by ovariohysterectomy; recurrence of tumor should be treated with surgery whenever possible. Radiation therapy—rarely considered due to excessive local disease and metastatic behavior.

	Chemotherapy—doxorubicin and cyclophosphamide reported to reduce metastatic disease; mitoxantrone may be helpful in some cases (see protocols 2, 4, and 7).

Mammary Tumors in Dogs

Common Clinical Signs:	Presence of a mass in the mammary chain.
Common Histologic Types:	Approximately 50% are benign (e.g., fibroadenomas, simple adenomas, and benign mixed mammary tumors); approximately 50% are malignant (e.g., solid carcinomas and tubular or papillary adenocarcinomas).
Biological Behavior:	Most common neoplasm in females; average age is 10–11 years; poodles, terriers, cocker spaniels, and German shepherds are overrepresented; early ovariohysterectomy protective; 50% of tumors are multiple; lungs and lymph nodes are most common sites of metastasis.
Prognostic Findings:	German shepherds have a poor prognosis; poor prognosis is

	associated with increasing tumor size, ulceration, degree of invasion, increasing degree of malignancy, lymph node involvement, and lack of hormone receptors.
Treatment Considerations:	Surgery—regional resection of tumor is as effective as mastectomy for localized tumor(s); removal of lymph node may be of prognostic value; ovariohysterectomy may not be of value for preventing recurrence.
	Radiation therapy—unproven efficacy; may be considered in the palliation of inflammatory carcinomas.
	Chemotherapy—doxorubicin- or mitoxantrone-based protocols may be effective in some cases (see protocols 1, 2, 4, and 7).

Mast Cell Tumors in Cats

Common Clinical Signs:	Cutaneous—single or multiple raised hairless masses.
	Lymphoreticular—splenomegaly and chronic vomiting.

	Intestinal—chronic vomiting or diarrhea.
Common Histologic Types:	Cutaneous tumors are usually well differentiated; lymphoreticular and intestinal tumors are malignant.
Biological Behavior:	Histiocytic cutaneous mast cell tumors in Siamese may regress spontaneously; lymphoreticular and intestinal tumors are always malignant; cutaneous tumors are often benign, even multiple tumors; may occur in young animals.
Prognostic Findings:	None identified.
Treatment Considerations:	Cutaneous—surgery, radiation therapy, with or without corticosteroids, for invasive lesions.
	Lymphoreticular—splenectomy gives 12-month median rate of survival.
	Intestinal: wide resection, with or without corticosteroids, but survival is poor
	Chemotherapy—unproven efficacy but may consider protocol 8.

Mast Cell Tumors in Dogs

Common Clinical Signs:	Raised or ulcerated intracutaneous mass; may be hairless or haired; may be single or multiple. Mast cell tumors can look and feel like anything.
Common Histologic Types:	Histologic grade influences surgical prognosis. Moderately differentiated (grade II) tumors are the most common.
Biological Behavior:	Boxers, Boston terriers, and golden retrievers are predisposed but can occur in any breed, at any age; metastasis is similar to other hematopoietic tumors, to regional lymph nodes as well as liver, spleen, and bone marrow.
Prognostic Findings:	Tumors on limbs have better prognosis than those on the trunk (especially perineum); slow growth and long duration of presence may be favorable; most important prognostic factor is histologic grade.
	Recurrence rate 6 months after incomplete-excision surgery—25% for well-differentiated tumors;

	44% for moderately differentiated tumors; 76% for poorly differentiated tumors.
Treatment Considerations:	Well-differentiated to moderately-differentiated tumors—wide surgical excision; adjunctive radiation therapy (88% achieve 5-year control for moderately differentiated tumors); although efficacy is uncertain, recent use of CCNU or Velban have shown promise. Poorly differentiated tumors—surgery, with or without radiation therapy, is palliative; H2 blockers, prednisone, and vincristine chemotherapy may be helpful (see protocol 8).

Mesothelioma in Dogs

Common Clinical Signs:	Effusion of body cavities causing abdominal discomfort, tachypnea, and respiratory distress; in decreasing order of incidence—affects pleural, peritoneal, or pericardial cavities.
Common Histologic Types:	Epithelial-type mesothelioma.

Biological Behavior:	Old dogs; exposure to asbestos and pesticide powders may be associated with development of mesothelioma in dogs.
Prognostic Findings:	None identified.
Treatment Considerations:	Chemotherapy—intracavitary cisplatin may provide palliation; responses to intravenous doxorubicin and mitoxantrone have been noted (see protocols 1–4).

Multiple Myeloma in Cats

Common Clinical Signs:	Nonspecific clinical signs; most cats are anemic; lytic bone lesions are rare.
Common Histologic Types:	Mature plasma cells.
Biological Behavior:	Old cats; mostly domestic shorthair; no association with FeLV.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—rarely considered. Radiation therapy—radiation-sensitive tumor; excellent local palliation of signs and complete remissions reported; guarded prognosis due to systemic nature of disease.

	Chemotherapy—remission rates of 40% with a median survival of 170 days reported in clinical cases treated with prednisone and an alkylating agent (melphalan, Cytoxan, Leukeran); consider as adjunct to radiation therapy in some patients.

Multiple Myeloma in Dogs

Common Clinical Signs:	Anemia and secondary infections due to myelophthisis; lameness and pain from bone lytic lesions; polyuria and polydipsia from hypercalcemia, renal disease, and paraproteinuria; hemorrhage due to hyperviscosity.
Common Histologic Types:	Mature plasma cells.
Biological Behavior:	Median age is 8–9 years; most cases occur in purebred dogs; systemic disease.
Prognostic Findings:	Dogs with hypercalcemia, extensive bone lysis, or light-chain (Bence Jones) proteinuria have a worse prognosis.

Treatment Considerations:	Surgery—rarely considered; used to palliate neurologic signs (paralysis) due to vertebral disease. Radiation therapy—radiation-sensitive tumor; excellent local palliation of signs and complete remissions reported; guarded prognosis due to systemic nature of disease. Chemotherapy—prednisone is palliative only; median survival is 220 days; melphalan and prednisone provide complete remission in 40% and partial remission in 50% of dogs for a median survival of 540 days; other agents, such as cyclophosphamide or chlorambucil, may be effective; consider chemotherapy adjunct to radiation therapy.

Myelodysplasia in Dogs and Cats

Common Clinical Signs:	Reflects cytopenias, such as fever and neutropenia or petechiation and thrombocytopenia.

Common Histologic Types:	Differentiated from leukemias by <30% blasts in a dysplastic bone marrow.
Biological Behavior:	No age, gender, or breed predilection; usually progresses to an acute leukemia in cats (most are FeLV antigenemic).
Prognostic Findings:	None identified.
Treatment Considerations:	Supportive treatment—antibiotics and transfusions of blood, blood products, or cytokines (Epogen, Neupogen). Chemotherapy—cytosine arabinoside (ara-C) and retinoids are under investigation as differentiating agents.

Nasal Tumors in Cats

Common Clinical Signs:	Epistaxis, sneezing, facial deformity, and epiphora.
Common Histologic Types:	Carcinoma and lymphoma.
Biological Behavior:	Old males (8–10 years of age); locally invasive and rarely metastasizes to distant sites until late in the course of the disease.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—contraindicated. Radiation therapy—treatment of choice; survival time for non-hematopoietic malignancies is 20–27 months; median survival time for cats with nasal lymphoma approaches 16 months. Chemotherapy—recommended for nasal lymphoma due to systemic disease (see protocols 6, 7, and 10).

Nasal Tumors in Dogs

Common Clinical Signs:	Unilateral epistaxis, facial deformity, and epiphora.
Common Histologic Types:	Adenocarcinoma.
Biological Behavior:	Most common in old dogs; no breed or sex predilection; tumor is locally invasive and rarely metastasizes to distant sites until late in the course of the disease.
Prognostic Findings:	Brain involvement is a poor prognostic sign.

Treatment Considerations:	Surgery—contraindicated unless combined with radiation therapy. Radiation therapy—with or without surgery, the treatment of choice; median survival rates vary from 8 to 23 months. Chemotherapy—cisplatin is reported to be effective in palliating clinical signs; mitoxantrone is used concurrent with radiation therapy to improve radiation efficacy (survival times exceeding 2 years).

Nonosteosarcoma Bone Tumors in Dogs

Common Clinical Signs:	More often affects axial skeleton than appendicular skeleton; care is required in interpreting incisional biopsy specimens.
Common Histologic Types:	Chondrosarcoma, fibrosarcoma, and hemangiosarcoma.
Biological Behavior:	Old dogs, except oral fibrosarcoma, in which younger dogs predominate; metastases occur at lower rate than with osteosarcoma and may occur late in the course of the disease.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—palliative; may be curative in some dogs, although metastases may arise even months or years after surgery. Radiation therapy—may improve tumor control; palliative for bone pain. Chemotherapy—unproven efficacy but consider protocols similar for osteosarcoma to prevent or delay complications arising from metastatic disease (see protocols 1–4).

Ocular Tumors in Cats

Common Clinical Signs:	Buphthalmos, poor vision, iris pigment change, and glaucoma.
Common Histologic Types:	Melanoma; less commonly, ocular sarcoma.
Biological Behavior:	Melanomas are malignant and have high metastatic potential; old cats usually are affected; no association with breed, gender, or FeLV status; sarcomas (often preceded by ocular trauma) are highly malignant.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—enucleation should be performed early in course of disease for melanoma; increasing degree of ocular involvement is associated with poorer survival. Radiation therapy—may improve local control, but melanoma and ocular sarcoma have high metastatic rates. Chemotherapy—unproven efficacy; low dosage weekly carboplatin has significantly improved survival in dogs with melanoma and may have efficacy in cats (see protocol 5).

Ocular Tumors in Dogs

Common Clinical Signs:	Glaucoma, uveitis, hyphema, or visible mass.
Common Histologic Types:	Melanoma; less commonly, epithelial tumors of the ciliary body.
Biological Behavior:	Melanomas and epithelial tumors have low potential for metastasis; old dogs are affected.

Prognostic Findings:	High mitotic index may indicate potential for metastasis in melanoma.
Treatment Considerations:	Surgery—enucleation is usually curative, even after failure of local excision; other treatment modalities are generally not required. Chemotherapy—unproven efficacy, possibly consider piroxicam or tamoxifen as palliative therapy.

Oral Tumors in Cats

Common Clinical Signs:	Halitosis, bleeding from mouth, and dysphagia.
Common Histologic Types:	Squamous cell carcinoma is the most common, followed by fibrosarcoma and acanthomatous epulis.
Biological Behavior:	Old cats; sublingual squamous cell carcinoma is more common than gingival squamous cell carcinoma.
Prognostic Findings:	None identified.
Treatment Considerations:	The efficacy of multimodality therapy (surgery, radiation therapy, and chemotherapy) greatly exceeds any single modality

approach. Consider protocols 2 and 4 adjunctive to radiation or surgery.

Oral Tumors in Dogs

Common Clinical Signs:	Oral mass, bleeding from the mouth, and dysphagia.
Common Histologic Types:	Benign—fibromatous epulis; acanthomatous epulis (may invade bone).
	Malignant—melanoma, squamous cell carcinoma, and fibrosarcoma.
Biological Behavior:	Melanoma—high metastatic rate; old dogs.
	Squamous cell carcinoma—moderately metastatic; lingual and tonsillar types are highly metastatic; old dogs.
	Fibrosarcoma—low metastatic rate, young dogs.
	Epulides—do not metastasize; all ages.
	All tumor types—small tumors and rostral location have a better prognosis.

Prognostic Findings:	Melanoma—low mitotic index is associated with a better prognosis.
	Squamous cell carcinoma—dogs with maxillary tumors and young dogs have a better prognosis.
Treatment Considerations:	Surgery—mandibulectomy or maxillectomy for local control of malignant tumors.
	Radiation therapy—curative for acanthomatous epulis; coarse fractionation may be useful for melanoma; adjunctive for squamous cell carcinoma and fibrosarcoma after surgery gives good control.
	Chemotherapy—platinum compounds are best for melanoma, 50% report 1 year survival times; chemotherapy is not usually required for other tumor types; see protocols 2, 4, and 5.
	Biological response modifiers—piroxicam and tamoxifen have anecdotal efficacy for dogs with melanoma and squamous cell carcinoma.

Osteosarcoma of the Appendicular Skeleton in Dogs

Common Clinical Signs:	Lameness and pain at metaphyseal sites, particularly distal radius, proximal humerus, proximal tibia, and distal femur; lytic and productive bone lesion on radiographs.
Common Histologic Types:	Osteoblastic osteosarcoma is most common; other diagnoses are possible—chondroblastic, telangiectic, and fibroblastic.
Biological Behavior:	Large to giant breeds; no sex predilection; usually middle-aged to old dogs; metastasis occurs early but may not be clinically evident.
Prognostic Findings:	Survival is poor; prognosis is uncorrelated with gender, tumor site, or whether a presurgical biopsy is performed.
Treatment Considerations:	Surgery—with amputation alone, median survival is 162 days; 11% of dogs are alive at 1 year; limb sparing provides good limb function for distal radius tumors. Radiation therapy—radiation-sensitive tumor but curative intent protocols rarely are considered

due to poor prognosis; palliative use for pain control as an alternative to amputation is considered good, median duration of pain control is 8 months.

Chemotherapy—regardless of limb removal, various chemotherapy protocols have shown efficacy in prolonging survival time. Cisplatin or carboplatin (protocol 3) shows 40–60% of dogs alive at 1 year; doxorubicin (protocol 1) shows 50% of dogs alive at 1 year; combination (protocol 2) shows 50% of dogs alive at 18 months.

Osteosarcoma of the Axial Skeleton in Dogs

Common Clinical Signs:	Tumors of the appendicular skeleton are four times more common than axial tumors.
Common Histologic Types:	Multilobular osteochondroma and osteosarcoma.
Biological Behavior:	Old dogs (except rib tumors, which often affect young dogs); no breed predilection; more females may be affected; highly metastatic,

	but local recurrence is more of a problem; mandibular osteosarcoma may have lower metastatic rate.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—difficult due to location of tumors; mandible and rib tumors can be resected.
	Radiation therapy—may be useful adjunct to surgery to reduce local recurrence or for palliation of pain.
	Chemotherapy—recommended for osteosarcoma of all sites (see protocols 1–3).

Ovarian Tumors in Cats

Common Clinical Signs:	Irregular or prolonged estrus.
Common Histologic Types:	Granulosa cell tumor.
Biological Behavior:	Mainly domestic shorthairs; ovarian tumors are rare tumors.
Prognostic Findings:	None identified.

Treatment Considerations:	Surgery—rarely curative because of high metastatic rate of all tumor types. Radiation therapy—unproven. Chemotherapy—unproven.

Ovarian Tumors in Dogs

Common Clinical Signs:	Abdominal mass or swelling; unexplained or abnormal estrus or bleeding.
Common Histologic Types:	Adenomas and adenocarcinomas.
Biological Behavior:	Old dogs (median age is 10 years); teratomas occur in young dogs.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—surgical excision curative for most tumors. Chemotherapy—consider protocols 1–4 adjuvant to surgical excision if carcinomatosis observed.

Peripheral Nerve Sheath Tumors

Common Clinical Signs:	Slowly progressive lameness.

Common Histologic Types:	Dogs—neurofibrosarcoma. Cats—lymphoma.
Biological Behavior:	Dogs—large-breed dogs; middle-aged dogs (average age is 7 years); local disease, rare metastasis. Cats—systemic disease.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—surgical resection of tumor for small masses; amputation and resection for large masses or if severe neurologic deficits are present; complete excision is difficult, recurrences are common. Radiation therapy—used for incompletely excised tumors, disease-free times can exceed 2 years. Chemotherapy—most effective for lymphoma; not necessary for soft tissue variants.

Prostatic Tumors in Dogs

Common Clinical Signs:	Tenesmus, constipation, dyschezia, and less commonly, dysuria and hematuria.
Common Histologic Types:	Adenocarcinoma.

Biological Behavior:	Equal frequency in castrated and intact dogs regardless of age at castration; old dogs (median age is 10 years).
Prognostic Findings:	May be more aggressive in castrated dogs but highly malignant in both castrated and intact dogs.
Treatment Considerations:	Surgery—difficult because of anatomy of canine prostate. Radiation therapy—palliative only, due to high metastatic rate. Chemotherapy—has no proven efficacy. Hormonal therapy—ineffective because of hormone independence of canine prostatic carcinoma.

Renal Tumors in Cats

Common Clinical Signs:	Nonspecific; hematuria rare.
Common Histologic Types:	Lymphoma, then adenocarcinoma.
Biological Behavior:	Old cats; no gender or breed predisposition; nephroblastoma can occur in young cats but is rare.

Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—rarely reported; carcinomas may have high metastatic rate.
	Chemotherapy—renal lymphoma may respond to combination chemotherapy (see protocols 6, 7, and 10).

Renal Tumors in Dogs

Common Clinical Signs:	Often no clinical signs; hematuria with transitional cell carcinoma.
Common Histologic Types:	Carcinomas and adenocarcinomas.
Biological Behavior:	Old dogs, usually males; nephroblastoma in young dogs; German shepherds may have cystadenocarcinomas and nodular dermatofibrosis on an inherited basis.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—high metastatic rate for carcinomas makes cure unlikely; early removal of nephroblastoma may be curative.
	Chemotherapy—reported only for nephroblastoma; vincristine, doxorubicin, and actinomycin D may

be palliative (consider protocols 1–4).

Retrobulbar Tumors in Cats

Common Clinical Signs:	Exophthalmos or enophthalmos.
Common Histologic Types:	Primary retrobulbar tumors are rare; extension of oral squamous cell carcinoma; nasal tumors and lymphoma.
Biological Behavior:	Old cats; behavior varies with tumor type.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—rarely useful as a primary modality, as most tumors have grown by extension from other sites; oral squamous cell carcinoma is unresponsive to surgery. Radiation therapy—may be a useful adjunct for squamous cell carcinoma when used in combination with mitoxantrone chemotherapy or for nasal tumors (consider protocol 4). Chemotherapy—may be useful for retrobulbar lymphoma, with or

without radiation therapy (see protocols 6 and 7).

Retrobulbar Tumors in Dogs

Common Clinical Signs:	Exophthalmos, nicitans protrusion, and deviation of globe.
Common Histologic Types:	Multiple types; osteosarcoma, fibrosarcoma, mast cell tumors, and lymphoma are most common.
Biological Behavior:	Most tumors are locally aggressive; metastatic rate varies with tumor type.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—orbitectomy may be curative for small tumors.
	Radiation therapy—should be useful as an adjunct to surgery for all tumor types but is still under investigation.
	Chemotherapy—may be useful for lymphoma; consider protocols 1–4 as adjunct to local modalities for treatment of osteosarcoma and osteochondrosarcoma.

Salivary Gland Tumors in Dogs and Cats

Common Clinical Signs:	Cervical mass; anorexia or dysphagia is possible.
Common Histologic Types:	Adenocarcinoma.
Biological Behavior:	May be diffuse oral tumor rather than a mass; metastasis may be more common in cats than dogs; old animals affected (median age is 10 years); poodles and Siamese cats are predisposed.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—high rate of local recurrence in cats and dogs. Radiation therapy—when used as an adjunct to surgery, radiation therapy seems to improve local control in dogs; presumably the same in cats. Chemotherapy—unproven efficacy but should be considered in cats due to aggressive behavior; consider protocols 2–4.

Soft Tissue Sarcoma in Dogs and Cats

Common Clinical Signs:	Subcutaneous firm and irregular mass appears (but is not) encapsulated.
Common Histologic Types:	Fibroma, fibrosarcoma, hemangiopericytoma, neurofibroma, neurofibrosarcoma, schwannoma, rhabdomyoma, rhabdomyosarcoma, leiomyoma, leiomyosarcoma, and malignant fibrous histiocytoma.
Biological Behavior:	Young cats; may be related to FeSV and FeLV infection; possible correlation with vaccination site in cats; locally invasive with a low metastatic rate.
Prognostic Findings:	Wide surgical excision at first surgery; metastasis is uncommon.
Treatment Considerations:	Surgery—wide surgical excision with cancer-free margins rarely results in cure. Radiation therapy—adjuvant external beam radiation therapy of >50 Gy gives control of 70–90% at 1 year.

	Chemotherapy—doxorubicin-based protocols and intralesional methods are being investigated; consider protocols 2–4 as adjunct to surgery or concurrent with radiation therapy.

Spinal Tumors in Dogs

Common Clinical Signs:	Pain; slow onset of ataxia and paresis.
Common Histologic Types:	Extradural tumors; vertebral body most common.
Biological Behavior:	Large-breed dogs, young to middle-aged; locally invasive.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice for extradural and intradural-extramedullary tumors; intramedullary tumors are not amenable to surgical excision.
	Radiation therapy—may be a useful adjunct to incomplete surgery.
	Chemotherapy—rarely considered unless tumor is of lymphoid origin.

Spinal Tumors in Cats

Common Clinical Signs:	Acute paresis.
Common Histologic Types:	Lymphoma.
Biological Behavior:	70% of cats are FeLV positive and 85% have bone marrow that contains lymphoma; most tumors are extradural.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—rarely indicated because of systemic disease. Radiation therapy—may give local palliation. Chemotherapy—in general, gives a poor response; best when used in combination with radiation therapy; consider protocol 6, 7, or 10.

Splenic Hemangiosarcoma in Dogs

Common Clinical Signs:	Palpable abdominal mass; hemoperitoneum; anemia; shock; and possibly collapse.
Common Histologic Types:	Hemangiosarcoma.

Biological Behavior:	Average age is 10 years; German shepherds are predisposed; metastasis may be confined to abdominal cavity if no concurrent right atrial lesion exists.
Prognostic Findings:	Ruptured viscera, hemoperitoneum, coagulopathy, signs attributable to anemia are poor prognostic signs.
Treatment Considerations:	Surgery—palliative without gross metastases, but survival is short. Radiation therapy—considered palliative for some lesions. Chemotherapy—prolongs survival; most protocols result in a median survival time of 12–15 months; consider protocols 1–4 and 7.

Splenic Tumors in Dogs

Common Clinical Signs:	Abdominal swelling and weakness; palpable abdominal mass.
Common Histologic Types:	Leiomyosarcoma, osteosarcoma, and fibrosarcoma.
Biological Behavior:	Average age is 11 years; no breed or gender predilection; metastasis commonly occurs to abdominal sites.

Prognostic Findings:	Ruptured viscera, hemoperitoneum, coagulopathy, signs attributable to anemia are poor prognostic signs.
Treatment Considerations:	Surgery—palliative without gross metastases, but survival is short. Radiation therapy—considered palliative for some lesions. Chemotherapy—prolongs survival; most protocols result in a median survival time of 12–15 months; consider protocols 1–4 and 7.

Stomach Tumors in Dogs

Common Clinical Signs:	Chronic vomiting, weight loss, and inappetence.
Common Histologic Types:	Adenocarcinoma; less commonly, leiomyomas; most common in lower two thirds of stomach.
Biological Behavior:	Old, male dogs; tumors cause ulceration and commonly metastasize to perigastric lymph nodes or viscera.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—tumors are usually diffuse and have metastasized at

	the time of diagnosis; therefore, aggressive surgery is rarely successful; recurrence is common.
	Radiation therapy—unproven.
	Chemotherapy—unproven.

Synovial Cell Sarcoma in Dogs

Common Clinical Signs:	Lameness and palpable mass.
Common Histologic Types:	Fibroblastic cell type.
Biological Behavior:	Middle-aged dogs; medium to large breeds; predominately male dogs; predilection for the stifle.
Prognostic Findings:	Mitotic index has prognostic value.
Treatment Considerations:	Surgery—amputation, better than 75% chance of 3-year survival.
	Radiation therapy—anecdotal responses reported in soft tissue tumors; provides pain palliation in those with substantial bony involvement.
	Chemotherapy—inadequately studied; cisplatin or combination of doxorubicin and cyclophosphamide may be helpful; consider

protocols 1–4 and 10 adjunctive to surgery or radiation therapy.

Testicular Tumors in Dogs

Common Clinical Signs:	Palpable mass in normal or atrophic testis; many are not palpable; feminization changes with some Sertoli cell tumors and seminomas.
Common Histologic Types:	Seminomas, Sertoli cell tumors, and interstitial cell tumors.
Biological Behavior:	Seminomas and Sertoli cell tumors have a high incidence in retained testes; old dogs; no breed predilection.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—usually curative as metastatic rate is low. Radiation therapy—may achieve long-term control for metastatic seminoma to sublumbar lymph nodes. Chemotherapy—no reports of chemotherapy for metastatic tumors.

Thymoma in Cats

Common Clinical Signs:	Dyspnea due to pleural effusion or large mass.
Common Histologic Types:	Malignant epithelial component with mature lymphocytes and mast cells.
Biological Behavior:	Old cats; no association with FeLV; tumors are usually encapsulated; paraneoplastic syndromes include myasthenia gravis, but this is less common than in dogs.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—treatment of choice in cats, may be curative. Radiation therapy—long-term remissions (>2 years) in nonsurgical patients. Chemotherapy—palliative responses observed using weekly vincristine therapy.

Thymoma in Dogs

Common Clinical Signs:	Cough; less commonly, dyspnea and lethargy; may have aspiration pneumonia secondary to myasthenia gravis and megaesophagus.

Common Histologic Types:	Epithelial malignant component associated with mature lymphocytes and mast cells.
Biological Behavior:	Old dogs; females possibly predisposed; usually large, invasive, slow-growing tumors with low metastatic rate.
	Paraneoplastic syndromes—myasthenia gravis is most common; polymyositis, hypercalcemia, and second malignancies may occur.
Prognostic Findings:	Dogs with megaesophagus have a very poor prognosis.
Treatment Considerations:	Surgery—may be curative for small or encapsulated tumors; dogs with megaesophagus need to be monitored for aspiration pneumonia; most thymomas are unresectable.
	Radiation therapy—long-term remissions (>2 years) in nonsurgical patients.
	Chemotherapy—palliative responses observed using weekly vincristine therapy.

Thyroid Tumors in Cats

Common Clinical Signs:	Hyperthyroidism with associated cardiac and hypermetabolic changes; peritracheal mass may be palpable.
Common Histologic Types:	Adenoma; carcinomas are rare.
Biological Behavior:	Old cats; no gender or breed predisposition.
Prognostic Findings:	None identified.
Treatment Considerations:	Supportive treatment—for example, propranolol and diltiazem, particularly for cardiac conditions.
	Medical management—methimazole and carbimazole reduce circulating thyroid hormone levels, but long-term use requires dosage increase.
	Surgery—as tumors are often bilateral, both glands should be removed; hypoparathyroidism or hypothyroidism may occur but is usually of short duration.
	Radiation therapy—radioactive iodine (^{131}I) gives good response

with prolonged remissions and few side effects; may also palliate effects of thyroid carcinoma.

Thyroid Tumors in Dogs

Common Clinical Signs:	Mass in ventral neck; rarely signs of hyperthyroidism.
Common Histologic Types:	Adenocarcinoma.
Biological Behavior:	Old dogs; no gender predilection; beagles, golden retrievers, and boxers are predisposed; local invasion is common; moderate metastatic rate.
Prognostic Findings:	Dogs with invasive tumors ("fixed" to underlying tissues) or large tumors predict worse survival rates; not correlated with histologic type, age, breed, or gender.
Treatment Considerations:	Surgery—curative for adenomas; may provide long-term control for small, noninvasive carcinomas, but these have potential to metastasize.
	Radiation therapy—external beam radiation may improve local control or reduce size of mass before

surgery; radioactive iodine (^{131}I) may cause regression in active hormonal tumors, which are rarely seen in dogs.

Chemotherapy—significant control of metastatic lesions observed with platinum-based protocols; consider protocols 1–4.

Hormonal therapy—anecdotal reports of long-term palliation of metastatic lesions (>1 year) seen with thyroxine supplementation.

Transmissible Venereal Tumor in Dogs

Common Clinical Signs:	Bleeding mass on external genitalia.
Common Histologic Types:	Transmissible venereal tumor.
Biological Behavior:	Spread by coitus and canine social behavior; females more susceptible than males; spontaneous regression in most cases after months, but not in immunosuppressed animals; rare metastasis.
Prognostic Findings:	None identified.

Treatment Considerations:	Surgery—curative if wide excision and localized tumor.
	Radiation therapy—low doses (10 Gy); may be curative if localized.
	Chemotherapy—weekly vincristine for 5–6 weeks may provide cure in 90% of dogs.

Vaginal and Uterine Tumors in Dogs and Cats

Common Clinical Signs:	Signs due to pelvic or urethral obstruction.
Common Histologic Types:	Leiomyoma and fibroma.
Biological Behavior:	Rare tumors, usually benign; often associated with ovarian cysts and endometrial hyperplasia.
Prognostic Findings:	None identified.
Treatment Considerations:	Surgery—may be curative for benign lesions.
	Radiation therapy—radiation-sensitive tumor; excellent responses observed.

4

Principles of Chemotherapy

When Should Chemotherapy Be Considered?

When considering the use of chemotherapy in the tumor-bearing patient, the approach to therapy will depend greatly on the therapeutic intent. Will the therapeutic goal be a cure or palliation? It is important to determine the goal clearly at the outset. A cure is the ideal outcome but not necessarily realistic in most cases or likely to be achieved unless it is the initial intent. If a cure is the intended outcome, aggressive therapy may provide substantial long-term benefit and a relatively high level of short-term toxicity may be justified. More commonly, the accepted goal of cancer therapy in

veterinary medicine is palliation. Toxicity to chemotherapy is minimized in an attempt to prolong an acceptable quality of life.

Although localized primary tumors, which are at minimal risk for metastasis, are most commonly treated with surgery or radiation or both, chemotherapy may occasionally be used instead of or in addition to standard local therapy. Systemic chemotherapy is also indicated following local treatment for adjunctive therapy in tumors that are commonly widespread or demonstrate a high rate of metastatic behavior (e.g., osteosarcoma or oral melanoma).

Tumor Growth and Response to Chemotherapy

An understanding of cell growth, the biologic behavior of tumors, and the metastatic pattern of specific tumor types is essential prior to formulating a treatment plan. The phases of the cell cycle are S, in which new DNA is synthesized; gap G_1, a period of RNA and protein synthesis; M, when the cell undergoes mitosis; and a second gap, G_2. The duration of each phase varies for different cell types. Resting cells, G_0, may retain the capacity to divide on proper stimulation. Normal and neoplastic cell populations are composed of both proliferating and resting cells; the proportion and the rate of cell death vary with the tissue type. Growth fraction is the proportion of

a population of cells actively proliferating, in contrast to those that are viable but quiescent. This concept must be distinguished from growth rate, the increase in size of the tumor over time.

It is helpful to consider the rate of growth of a tumor more in terms of doubling time than in terms of size per time. Doubling time refers to the time required for number of cells to double, which is clinically evident as volume. Some tumors are anatomically difficult to characterize; however, most can be assumed to be roughly spherical for purposes of calculation.

The smallest clinically detectable tumor generally has a mass of 1 g, about 1 cm diameter, and contains approximately 10^9 cells. If a tumor is assumed to have originated from a single cell, then it has already undergone 30 doublings by the time it is clinically detected. To increase in size to 1 kg theoretically takes only another 10 doublings, assuming that all cells survive. Therefore, the majority of the lifespan of a tumor is probably spent in the subclinical phase.

Depending on the growth fraction and the rate of cell death, normal cell growth is classically thought of as an exponential phenomenon in which the rate of doubling of the population remains fixed over time. Tumor cell populations, however, tend to adhere more closely to Gompertzian kinetics, meaning that the doubling time tends to increase exponentially over time then reach a plateau phase. The plateau phase is most likely due to a

decrease in the growth fraction due to hypoxia, depletion of nutritional factors, and an increase in the rate of cell death rather than an increase in the length of the cell cycle.

In general, the higher the growth fraction of a population of cells, the more chemosensitive they are expected to be. This explains why the most common side effects of chemotherapy are gastrointestinal disturbances and bone marrow suppression, since these populations are constantly proliferating. Likewise, a tumor reaching the plateau phase of the growth curve due to hypoxia and poor cell nutrition is more chemoresistant than one in the exponential or linear phase.

Whether palliation or a cure is the therapeutic goal, the remission of tumors is desirable. Complete remission is specified as an inability to detect clinical evidence of tumor. This does not mean that all tumor cells have been removed. The remaining cells are a source of potential relapse or recurrence of the gross tumor. When relapse occurs during chemotherapy, it implies that the tumor is resistant to the agents being given.

Pharmacologic Principles of Chemotherapy

To induce remission without harming the patient, anticancer drugs must damage tumor cells to a greater degree than normal cells. Cytotoxicity is to the chemotherapeutic action of a drug. The mechanism of cytotoxicity varies with each drug class. In general,

however, efficacy is greatest against actively cycling cells, and some agents act specifically on cells in certain phases of the cell cycle. Knowledge of the mechanism of action for each drug allows the use of drug combinations that may act synergistically and avoidance of drugs that may antagonize each other's mechanism of action.

When a cytotoxic drug is administered to a population of cells, the number of cells killed will not be absolute but a percentage of the total number. If a tumor containing 10^9 cells is exposed to a dose of drug that kills 99% of the population, 9.9×10^8 cells will be killed and 10^7 will remain, but the tumor now will be clinically undetectable. If the tumor starts at a mass of 100 g, or 10^{11} cells, 9.9×10^{10} cells will be killed and 10^9 will survive; the drug has been equally effective but the tumor remains clinically detectable.

The cytotoxic action of chemotherapeutic agents depends on concentration over time rather than peak plasma levels, whereas peak plasma level often determines adverse effects on normal tissue. This makes the use of slow infusion techniques desirable for intravenous drugs.

Dose Response Curve

For all effective drugs, a sigmoid curve can be defined between the dose administered and the effect, such as percentage of cells killed. This curve exists for normal cells as well as tumor cells. An ideal drug has a response

curve with a steep slope for tumor cells and a gradual slope for normal cells; furthermore, the therapeutic dose should fall on the linear portion of the curve for tumor cells and at the foot of the curve for normal cells. Thus, a small increase in dose brings about a large increase in tumor response and a small increase in toxicity. The curve plateaus at a point of maximal effect, beyond which any further increase in dose will not increase the response.

Therapeutic Index

As with other medications, the therapeutic index refers to the ratio of the toxic dose to the effective antitumor dose. The therapeutic index of most chemotherapeutic agents is relatively low, necessitating careful dosing. Improvements in therapeutic index can be made by using techniques that either make the drug more effective or protect against toxic effects.

The optimum dose is at the point on the dose response curve where maximum antitumor effect and acceptable toxicity occur. It may be necessary to accept some toxicity or some risk of incomplete response or both. In practice, the optimum dose in a given circumstance depends on the goal of therapy. If the goal is a cure, toxic risks are likely. If palliation is the goal, toxicity will be avoided, but an incomplete response is likely.

Toxicity from chemotherapeutic agents ranges from mild to life threatening. Tissues with high growth

fractions such as bone marrow and epithelial tissues, including the gastrointestinal tract, normally are most susceptible to toxic side effects. Some drugs have additional toxic effects on other tissues, such as in the urinary tract, myocardium, or pancreas. These effects may be unrelated to the cytotoxic effects and idiosyncratic or species specific. Anaphylaxis is of concern in the use of certain drugs, as a reaction to either the drug itself or the carrier.

Drug Classes

The major classes of chemotherapy agents are the alkylating agents, antimetabolites, mitotic inhibitors such as plant alkaloids and podophyllotoxins, and antibiotics. Two additional important agents are the platinum compounds and the enzyme L-asparaginase. The alkylating agents are the largest, oldest group and are not cell cycle specific. The antibiotics have a variety of mechanisms of action; the most commonly used are the anthracyclines.

The toxic side effects of some chemotherapy agents can be specifically antagonized or minimized by the use of special administration techniques, such as saline diuresis before administration of cisplatin to minimize renal toxicity, or a second drug, which does not have direct antitumor effect but does allow the use of higher doses because of an increased therapeutic index. An example is the use of mesna to prevent hemorrhagic cystitis caused by ifosfamide.

Resistance to Chemotherapy

Tumors may be intrinsically resistant to anticancer drugs or they may acquire resistance as a result of exposure. A tumor cell may be naturally unaffected by the mode of action of a chemotherapeutic agent; the cell may not have receptors or activating enzymes for the drug or may not be reliant on the biochemical process with which the drug interferes. In addition, some anatomical locations are difficult to treat with chemotherapy because of the inability of the drug to reach the site of the tumor (e.g., blood-brain barrier). Furthermore, drugs may not reach all cells in a poorly vascularized tumor, and these cells may survive in a quiescent state to reemerge at a later time.

Acquired resistance develops after tumor cells have been exposed to a drug or similar class of drugs. Spontaneous mutation is assumed to be ongoing regardless of the presence of any drug and the occurrence of spontaneously resistant cells in a population approximates the rate of mutation. The rate of spontaneous genetic mutation in both normal and neoplastic cell populations is generally estimated at 10^{-7}–10^{-5} per mitosis. If the population then is exposed to the drug, the resistant cell will have a growth advantage. Many chemotherapy agents are mutagenic and may increase the risk of development of clones resistant to one or more drugs. Therefore, the larger the number of cells in a tumor, the more likely it is that spontaneous resistance will occur. If only a small

subset, or clone, has the resistant phenotype, it will eventually become the dominant cell type in the tumor because of the growth advantage conferred by its ability to grow in the presence of a given drug. Until the resistant clone reaches a certain size, this may not be clinically evident, if most of the tumor is sensitive. This is one mechanism of relapse.

Gene amplification is another source of acquired drug resistance enhanced by the presence of gradually increasing concentrations of the drug. Drugs, such as mitotic inhibitors, that promote a delay in the cell cycle just prior to the M phase are most likely to promote this phenomenon. A good example of acquired drug resistance by gene amplification is the multiple drug resistance phenotype. Multiple drug resistance (MDR) is a phenomenon of cross-resistance of cells to a variety of agents not structurally or functionally related. These include the antitumor antibiotics, podophyllotoxins, and the plant alkaloids. MDR is mediated by p-glycoprotein, a cell membrane pump that is present normally on the surface of some epithelial cells. The protein actively removes drug from the cell, making it resistant to any drugs that are substrates for the pump.

Chemotherapy Protocols

COMBINATIONS AND SCHEDULING Using drugs in combination maximizes therapeutic potential. The most important criterion for inclusion of a drug into a

combination protocol is efficacy as a single agent against the tumor in question. Using closely related drugs in combination usually does not improve efficacy significantly and may increase toxicity, whereas effective combinations generally consist of drugs that target different metabolic pathways. Some drugs are synergistic when used in combination, but often the effects are simply additive. Combinations allow the use of a higher total cytotoxic dose when the toxic effects of the individual drugs are different.

Scheduling of drug administration can be critical since giving it too late may markedly decrease the antitumor effect of a drug, either because the growth fraction of the tumor has decreased or a resistant clone has developed. Also, the scheduling of the various drugs in relation to each other is important. Differences and similarities in mode of action, toxicity, and mode of resistance should be considered.

It is critical to avoid overlapping the toxicity of the drugs in combination chemotherapy protocols. The most commonly encountered example of this is in the use of multiple myelosuppressive agents. The onset of the neutrophil nadirs of various drugs must be taken into account when planning the sequence and timing of therapy; and since some alkylating agents cause delayed myelosuppression, this may not be readily evident until a second drug is administered.

MULTIMODAL THERAPY Chemotherapy is often used successfully in combination with other therapeutic modalities, particularly surgery and radiation therapy. If multimodal therapy is to be used, the combination should be planned in advance rather than using different modalities one after the other as each one fails. Preoperative (neoadjuvant) chemotherapy is indicated when a primary tumor is so large that it is inoperable or involves vital structures. Usually, however, chemotherapy is used postoperatively (adjuvant) after incomplete excision or when micrometastases are expected to be present, based on a knowledge of the behavior of a particular tumor. In theory, adjuvant therapy should be particularly effective since the growth fraction of residual tumor is likely to be relatively large.

Dose Determination

Because the therapeutic index of chemotherapeutic agents is generally low, accurate dosing is imperative. Despite numerous examples in humans where clinical pharmacokinetics have been successfully applied to improve anticancer therapy, most veterinary anticancer drug dosages and regimens are based on human dose extrapolation and empirical trial and error. It is important, therefore, to realize there are specific species differences in metabolic rates and pathways (e.g., cisplatin-induced fatal pulmonary toxicity in cats but not in dogs).

Body surface area, an accurate reflection of metabolic rate, has been used to calculate drug dosage in humans. Most anticancer drugs prescribed in veterinary medicine are dosed on a per body surface area basis rather than a per weight basis for similar reasons. However, in recent times many veterinary oncologists have become aware that, in doing so, smaller-sized patients receive a much higher mg/kg dose than larger-sized patients. For example, when dosing doxorubicin on a per body surface area basis (30 mg/m^2, equivalent to 1 mg/kg), smaller-sized dogs (e.g., a 5-kg dog dosed at 30 mg/m^2 is given a dose equivalent of 1.74 mg/kg) have higher peak plasma concentrations, greater plasma drug concentrations versus time curves, longer drug elimination half-lives, greater volumes of distribution of the central compartment, more pronounced myelosuppression, and more clinical signs of toxicoses than larger-sized dogs.

Although these findings do not imply a carte blanche revision of anticancer drug dosages in veterinary medicine, application of knowledge regarding species variability in drug pathways, coupled with limited veterinary studies and phase I and II human pharmacokinetic studies should result in improved veterinary therapy compared to empiric trial and error.

Administration

Anticancer drugs have been given orally, intravenously, subcutaneously, topically, by an intracavitary or intravesicular route, and intraarterially. Efficacy and toxicity often vary based on the route of administration chosen. Care should be given to assure proper administration of all chemotherapy drugs. Only a few chemotherapy drugs are available in an oral form, but they are widely used in veterinary oncology, where frequent office visits for therapy and a perception of the pet's discomfort may deter the client from pursuing other equally or more important forms of treatment. When chemotherapeutic agents are dispensed for home use, the client must be made aware of the hazards associated with handling the drugs. Appropriate precautions should be taken to prevent human exposure, especially when children or adults of childbearing age are members of the household.

The intravenous route is readily accessible in most veterinary patients and is most commonly used. A few drugs can be extremely irritating if administered perivascularly (e.g., vincristine, doxorubicin), so care must be taken in using these drugs in animals that are difficult to restrain.

Only a few chemotherapy agents are available for intramuscular or subcutaneous administration. The use of a subcutaneously implanted continuous infusion or absorption devices holds great promise for drugs that are not irritating. Some drugs are actually less toxic when

given by the subcutaneous or intramuscular route. L-asparaginase is associated with a much lower rate of anaphylaxis when used intramuscularly than when given intravenously.

A few drugs are available in topical form for use in human medicine; however, these generally are not useful in veterinary medicine. Toxicity and poor efficacy have been encountered.

The use of intracavitary and intravesicular chemotherapy has applications in special cases where the tumor is not bulky, since the drug will penetrate only a few millimeters from the drug-cell interface. Examples of such tumors may include mesotheliomas, pleural or peritoneal carcinomatosis, and noninvasive transitional cell carcinomas. The drug used must be nonirritating. Since systemic absorption is likely, the dose should be within the safe systemic range.

If a major artery supplying a tumor can be identified and catheterized, some drugs may be given intraarterially to deliver a high concentration of drug to the tumor without exposing the host to an excessively high total body dose.

Chemotherapy Safety Guidelines

Concerns in the Workplace

Health concerns regarding occupational exposure to drugs used in cancer therapy are primarily associated

with those drugs referred to as *cytotoxic*. Beginning in the early 1980s, a series of Technical Assistance Bulletins have been developed by the American Society of Hospital Pharmacists and recommendations from the Federal Occupational Safety and Health Administration, the National Institutes of Health, the American Medical Association, and others to address the potential health hazards of low dose occupational exposure to cytotoxic anticancer drugs. Similar guidelines have been published in the veterinary literature. The potential danger to health care professionals from handling a cytotoxic drug stems from a combination of its inherent toxicity, individual susceptibility, concurrent exposure to known carcinogens, and the level and type of exposure. Exposure may occur through inadvertent ingestion of a drug in foodstuffs or cosmetics, inhalation of drug dusts or droplets, or direct skin contact. Health risks from low-level occupational exposure must be addressed as a reality, but the word *potential* must be used, since no conclusive evidence establishes an association between occupational exposure and disease. However, considerable controversy stems primarily from retrospective studies suggesting that nurses who handled cytotoxic drugs in an unprotected fashion had an increased risk of fetal loss. In addition, some cytotoxic drugs are mutagenic, teratogenic, or carcinogenic under laboratory or clinical conditions. Given the current level of concern and the need to protect veterinary professionals from potential

occupational health risks, many veterinary hospitals have instituted formal procedures for the safe handling of cytotoxic drugs in the workplace. Correct preparation and handling techniques prevent dust particles and liquid droplets from escaping into the workplace when cytotoxic drugs are being manipulated. Workplace contamination can also occur through accidental spills and breakage of drug containers. Although the need for caution and common sense when handling cytotoxic drugs is real, there is no justification for hysteria. Safety equipment and safe handling methods relating to cytotoxic drugs should be followed in the same way that safety equipment and safe techniques are accepted when operating X-ray equipment or handling infectious material. All hospital personnel who handle cytotoxic drugs should have training in the procedures and access to information pertaining to their responsibilities. As with other conditions in the workplace, "right to know" policies for health care professionals should be followed.

Drug Storage and Preparation

All chemotherapeutic drugs should be clearly identified as potentially hazardous.

Chemotherapeutic drugs requiring refrigeration should be stored separately. Store chemotherapeutic drugs in a properly marked zipper closure plastic bag or in a bin designed to contain accidental leaks. A good location for drug preparation is a side room away from

ward traffic and food preparation areas. Windows, doors, and air vents should be closed to eliminate drafts. No other activity should occur in the room during drug preparation and administration. Read the package insert prior to admixing any chemotherapeutic drug. Have the following materials and supplies readily available in the immediate work area: plastic-backed diaper, gauze pads, cotton balls, alcohol, gown, gloves, face mask, glasses or goggles, syringes, needles, venting pins, stopcocks, diluent, drug, zipper bags, pen or marker, sharps container, and hazard labels. Wash hands thoroughly prior to drug preparation.

Prepare drugs on a working surface at waist level. Use plastic-backed absorbent sheets to line the immediate work surface. During preparation wear a lint free disposable gown made with low permeability fabric. The gown should have a solid front, long sleeves, and snug fitting elastic cuffs. Wear two layers of talc-free latex gloves. Necropsy gloves are appropriate, since latex gloves may be less permeable to chemotherapeutic drugs than gloves made from polyvinyl chloride. Torn or punctured gloves should be discarded and not used. When wearing double gloves, one glove should be under the gown cuff and the other over it so no skin of the wrist or forearm is exposed. If clothes become contaminated do not wash them. This could expose others. Discard contaminated clothes in a properly marked container for chemotherapeutic waste. Wear a disposable face mask. Wear a pair of safety glasses or splash goggles.

Once the proper diluent and the correct amount have been determined, inject slowly into the chemotherapeutic drug vial. Surround the drug vial stopper with an alcohol-dampened 4 × 4-inch gauze pad prior to withdrawing the needle from the drug vial. Both needle and syringe should be withdrawn together. Discard the syringe and needle into an appropriate puncture-proof waste container. Do not recap the needle. When withdrawing admixed drugs from a drug vial, the syringe should be filled to no more than two thirds. Avoid large fluctuations between atmospheric pressure and pressure within vials. Venting devices can be useful for capturing aerosolized droplets that have resulted from sudden pressure changes. If multiple syringes are to be filled, the vial should be fitted with a stopcock. Use syringes and intravenous (IV) sets with Leur-lock fittings as a precaution against the accidental separation possible with standard friction fittings. Aspirating the fluid slowly may create fewer air bubbles in the syringe. Do not tap the syringe to concentrate air bubbles. This increases drug aerosolization. Injecting the bubbles into an alcohol-moistened cotton ball may safely eliminate those present.

Do not recap needles. Recapping, crushing, or clipping needles increases the risk of cutaneous or aerosolized drug exposure. Using venting devices to withdraw the admixed drug can minimize cutaneous exposure. Discard unused chemotherapeutic drugs into an appropriate chemotherapeutic drug waste container.

When breaking an ampule, wear protective gloves. This reduces the possibility of cutaneous absorption. Place an alcohol-dampened 4 × 4-inch gauze pad at the neck of the ampule. This will absorb any aerosolized drug. Remove the drug slowly from the ampule to minimize spillage or aerosolization. Inject excess air bubbles into an alcohol-moistened cotton ball.

Count tablets and capsule forms of chemotherapeutic drugs on separate counting trays from those used for other hospital drugs. Minimize reducing tablet size for the convenience of smaller-sized patients. Reducing tablet size may result in the aerosolization of drug dust.

After preparation has been completed, label all vials and bottles with the date and time. Seal reconstituted drugs that are ready for administration in a properly marked zipper closure bag or leakproof container for transport to the administration area. Place all broken ampules, needles, and other sharp items into a sealed puncture-proof container that is separate from other hospital trash. Clean the preparation area by discarding the plastic-backed absorbable paper liner and then washing the surface with soap and water. Use paper towels to dry this area. All contaminated clothing should be removed prior to leaving the work area. Discard all items in a properly marked waste container. Discard the gown and latex gloves. Thoroughly wash hands with soap and water to remove any possible drug residue. Remember hand washing is no substitute for wearing gloves; and if

medication is sent home with the patient, supply the owner with protective latex gloves.

Drug Administration

All drugs should be transported in a properly marked leakproof container or zipper closure bag. Prior to administration, double-check drug selection and dose calculations. All personnel involved in drug administration must wear protective gowns, gloves, and face apparel. When administering IV chemotherapeutic drugs, place a plastic-backed absorbent liner under the patient. Place an alcohol dampened 4 × 4-inch gauze pad under and around the IV injection port to prevent aerosolization of the drug. Monitor the administration set carefully for leaks. Administer IV chemotherapeutic drugs through a patent indwelling catheter that has been placed aseptically. Flush IV catheters with a solution compatible with the drug prior to and following chemotherapeutic drug administration. This information can be obtained from the drug insert. Cover the needle with a 4 × 4-inch gauze pad when removing the needle from the injection port.

Discard contaminated needles and syringes into a puncture-proof container designated only for chemotherapeutic drugs. Dispose of contaminated soft goods such as catheters, IV administrations sets, venosets, gloves, and gowns with other chemotherapeutic drug wastes. Although there is no evidence to date that exposure to

urinary or fecal waste from a patient receiving chemotherapeutic drugs is harmful, hospital personnel, as a regular part of the hospital clean hygiene plan, should always wear gloves when handling body wastes from patients. Ward cages or runs housing patients treated with chemotherapeutic drugs should display a warning label to alert hospital personnel. Body waste from chemotherapeutic patients should be disposed of with other biohazardous waste.

Drug Disposal

Written policies regarding the identification, containment, segregation, disposal, and collection of chemotherapeutic drug wastes should be established and posted in the workplace. All containers should carry a hazardous drug waste label. Segregate all chemotherapeutic-drug-contaminated waste containers from other hospital trash, and dispose of the waste according to local, state, and federal regulations. Frequently, human hospital pharmacies can be persuaded to accept the small amounts of waste generated by veterinary hospitals.

Accidental Spills

Place an accidental spill kit in the preparation and administration areas. The spill kit should contain an isolation gown made with low permeability fabric, two pairs of latex gloves or necropsy gloves, face mask, shoe covers,

eye goggles, cat litter, paper towels or absorbent pads, a hemostat, and a thick resealable plastic bag that carries an appropriate hazardous waste label. If an accidental spill occurs, restrict access to the area immediately and allow some time to pass to allow spilled drug to settle onto surfaces, decreasing the risk of aerosolized exposure. The spill then should be cleaned at once.

If a human or animal has become contaminated by the spill, the contaminated skin should be washed with soap and water and contaminated eyes should be flushed with an eyewash or water-based solution for a minimum of five minutes. A physician should be contacted immediately regarding additional emergency medical measures. Contaminated clothing must be removed and discarded with all other contaminated waste. One person should be designated for cleanup. Protective apparel must be worn and the spill kit used. Promptly obtain and wear the protective isolation gown, two pairs of latex examination gloves or heavy necropsy gloves, eye goggles, shoe covers, and face mask. Collect broken glass with a broad edge tray or hemostat and place into a separate puncture-proof container. Absorb liquids with disposable towels, pads, or cat litter. Collect powders with a damp disposable towel or pad. Rinse the contaminated surface with water and then clean with detergent. Do not use chemical deactivators. Detergent-cleaned surfaces should be cleaned again with water. Clean the spill area once more with soap and water and minimize use of this

area for 24 hours. Place all contaminated materials in a resealable, disposable thick, plastic bag that carries an appropriate warning label. Wash hands thoroughly after cleanup.

Use Common Sense

The preceding guidelines should be evaluated for suitability in each veterinary hospital. The costs of implementing all of the guidelines may be considered impractical in some situations. It is recommended that each veterinary hospital adopt some form of safety guidelines for handling chemotherapeutic drugs and review these with the hospital staff on a regular basis. Remember, common sense, good techniques, and inexpensive safety precautions should eliminate the likelihood of exposure. If you have additional questions, contact an oncologist or oncology technician in your area.

Management of Chemotherapy Side Effects

Prevention

Chemotherapy-associated complications should be and usually are rare events in veterinary oncology. The single most important method for avoiding chemotherapy toxicity is to know the potential side effects of the drugs you intend to use. Many complications are avoidable, and it

is imperative that research on utilization of these drugs be performed before use. It is also important to know any synergistic toxicity that may exist if a combination of chemotherapeutic agents (or other medications) is planned. Several texts contain valuable information about chemotherapeutic drug handling and toxicity, and veterinarians are encouraged to consult experienced individuals before using these agents. A complete blood count (CBC), serum biochemical panel, and urinalysis (UA) should be performed prior to the first chemotherapy treatment; and these tests should be repeated as necessary, depending on the drug administered. With rare exceptions, treatment with myelosuppressive agents should not be performed if the neutrophil count is less than 2,500 cells/μl or the platelet count is less than 100,000/μl (some individuals use 75,000/μl as a guideline for platelets). A urinalysis should be performed to rule out preexisting cystitis prior to use of drugs such as cyclophosphamide, to identify occult urinary tract infections (UTI), and to identify early renal dysfunction that may affect excretion of chemotherapeutic drugs. Renal dysfunction is an absolute and relative contraindication for use of cisplatin and carboplatin, respectively. Patients receiving doxorubicin should be carefully evaluated for cardiac disease (dog or cat) or renal disease (cat). Some veterinarians perform an electrocardiogram (ECG) prior to each treatment with doxorubicin. Others require thoracic radiography and echocardiography on patients at high

risk for cardiomyopathy or congestive heart failure (boxers, doberman pinschers, dogs with heart murmurs and cardiac silhouette or vessel abnormalities on thoracic radiography, or cats with heart murmurs) prior to administration of doxorubicin.

Chemotherapy administration should take place in an area of the hospital that is relatively traffic free to ensure full concentration of the staff administering chemotherapy as well as a calm environment for the patient. This may require that chemotherapy treatments be performed at a time of day that is less hectic than usual. You should be sure that all required materials are prepared ahead of time and additional materials are within easy reach. It is important to remember that many chemotherapy agents are dosed using the body surface area method. It is equally important to remember that the m^2 charts use body weight expressed in kilograms. It is a good practice to have chemotherapy doses determined by two individuals to verify calculations, and drug concentrations should be verified to ensure that final drug volumes are appropriate. At times, it is necessary to adjust chemotherapy dosages for individual patients. Doxorubicin and other drugs are sometimes dosed on a mg/kg basis for very small patients. Additionally, dosages should be decreased by 20–25% for those patients who experience side effects of severe gastrointestinal distress or marked myelosuppression.

Use of premedications varies considerably among those who administer chemotherapeutic drugs routinely.

Despite this variation in protocols, certain antineoplastic agents always require premedications. It is imperative to administer antiemetics to dogs prior to use of cisplatin. Butorphanol (0.4 mg/kg subcutaneously [SQ] or intramuscularly [IM] 30 minutes before cisplatin) or ondansetron (Zofran, 0.3 mg/kg continuous rate infusion [CRI] over 30 minutes just prior to administration of cisplatin) are commonly used for this purpose.

Most chemotherapy drugs have very specific routes of administration, and if not properly administered, disastrous results may ensue. Complications resulting from extravasation of vesicants and the requirement for saline diuresis with use of cisplatin are examples. In addition, it is important to know the difference in the degree of myelosuppression associated with various routes of administration and dosing schedules of chemotherapy agents. For example, a single subcutaneous dose of cytosine arabinoside results in less myelosuppression than administration of the same dose as a CRI over several hours. In contrast, administration of a single large dose of cyclophosphamide results in a greater degree of myelosuppression than dividing the same dose over several days. Avoid using peripheral veins for phlebotomy when possible. Only highly qualified staff members should be responsible for treating chemotherapy patients with drugs that are capable of causing extravasation reactions.

Venipuncture sites should be clipped adequately to allow visualization of the vein and prepared aseptically. Avoid sites of previous venipuncture that have taken

place within the prior 24 hours. Aspirate to check for good blood flow and flush the catheter well with at least 5 cc of nonheparinized saline solution prior to administration of the chemotherapeutic drug. After administration of the chemotherapy agent, do not aspirate back into the saline-filled syringe prior to flushing with the saline, as you will contaminate the flush with the chemotherapy drug. Various catheter types are utilized, chosen based on the drug to be administered, individual preference level, and patient characteristics. At times, it becomes necessary to place venous access ports to ensure appropriate administration of intravenous chemotherapy agents. The site of administration should be recorded for each treatment for future reference.

Histaminic (anaphylactoid) reactions are reported with the use of doxorubicin, L-asparaginase, and paclitaxel (Taxol). This toxicity is rarely observed with use of doxorubicin or L-asparaginase but prompts some veterinarians to premedicate with diphenhydramine (1 mg/kg in cats and 2 mg/kg in dogs SQ or IM 30 minutes prior to administration of chemotherapy drug) and dexamethasone sodium phosphate (dex SP, 0.5 mg/kg IV immediately prior). Premedication with these drugs is required when using Taxol due to the high incidence of these reactions, and some oncologists advise administration of oral prednisone the night before treatment in addition to the premedications just described. Histaminic reactions may be characterized by cutaneous erythema, pruritus, wheals, vomiting, vocalization, or cardiovascular

collapse (similar in nature and variability to the immune response elicited by beestings or vaccinations). If such a reaction occurs, chemotherapy administration should be discontinued and treatment with diphenhydramine, dex SP, with or without epinephrine initiated.

Acute vomiting is a rare side effect unless accompanying a histaminic reaction. One exception is emesis seen routinely following treatment with cisplatin unless pretreatment with butorphanol or ondansetron is performed as described previously. Cimetidine (4 mg/kg IM 30 minutes prior to chemotherapy) is given as an additional premedication when Taxol is administered to avoid vomiting secondary to histaminic gastritis. Other patients may require treatment with antiemetic medication immediately preceding or following administration of other antineoplastic agents. If a patient has exhibited vomiting as an acute or subacute side effect to drugs such as doxorubicin, administration of metoclopramide immediately preceding chemotherapy and for one to three days afterward may be warranted. Some veterinarians advise fasting chemotherapy patients before treatment in an effort to prevent nausea.

Subacute Toxicity

Subacute toxicity syndromes include myelosuppression, gastrointestinal disturbance, and sterile hemorrhagic cystitis. When highly myelosuppressive agents are administered (usually these drugs are given every 3–4 weeks), a

CBC should be obtained at the time of the first expected nadir (usually 10–14 days), to establish the degree of myelosuppression caused by the drug. Subsequent doses should be reduced by 20–25% if the neutrophil count is less than 1,000 cells/μl. If the neutrophil count is <1,000 cells/μl, administer prophylactic oral antibiotic therapy, usually trimethoprim-sulfa (22 mg/kg bid) or enrofloxacin (5 mg/kg bid). Sometimes, it is appropriate to instruct the clients to take their dog's temperature so that they are able to do this at home if the dog feels unwell. If neutropenia and fever or hemorrhagic feces are present simultaneously, then hospitalize the patient for IV antibiotic therapy: cephazolin (22 mg/kg tid–qid), with or without enrofloxacin (5 mg/kg IV sid), with or without metronidazole (7.5–10 mg/kg orally [PO] bid). Intravenous fluids may be administered if GI signs are severe or in an attempt to help diminish a febrile episode; the choice of IV fluids used varies with electrolyte and glucose requirements. Blood glucose levels should be evaluated for suspected septicemic patients. If the patient is suffering from severe lethargy or GI distress, a full biochemical profile should be performed to evaluate renal and hepatic function, as well as serum electrolyte levels. Urine should be collected to identify possible UTI and assess urine specific gravity, prior to initiation of fluid therapy, as a complement to blood urea nitrogen and creatinine to evaluate hydration status and renal function.

Use of granulocyte colony-stimulating factor (hrG-CSF, Neupogen) has become commonplace for neutropenic, febrile patients, though some clinicians reserve this treatment for those cases in which neutrophil rebound does not occur within 24–36 hours or those with neutrophil counts less than 500 cells/μl. The dose of hrG-CSF is 5 μg/kg SQ once daily. A daily CBC should be obtained until the neutrophil count is above 2,000 cells/μl (usually 1–3 days), at which time treatment with hrG-CSF is discontinued. Occasionally, oncologists initiate treatment with hrG-CSF at the time of the expected neutrophil nadir if a particularly myelosuppressive chemotherapy protocol is in use. It is important to remember that hrG-CSF should not be administered within the first few days following myelosuppresive therapy, as this places stem cells at risk for injury by the chemotherapy agent as they are stimulated to enter the cell cycle. Neutropenia-associated fever and sepsis is very rare in cats. Chemotherapy-associated anemia is generally mild and self-limiting. Treatment of chemotherapy-induced thrombocytopenia remains supportive in the form of blood transfusions if a bleeding diathesis causes severe anemia. Thrombopoietin (a bone marrow stimulatory factor for platelets) may become commercially available in the future and could prove useful in these patients.

Subacute vomiting is generally mild and self-limiting, and the usual recommendations are for fasting or

nothing by mouth, followed by small, frequent feedings of a bland diet. Use of antiemetic drugs, such as metoclopramide or chlorpromazine, may be initiated for patients with more than one episode of vomiting. It may be necessary to administer these drugs parenterally if the patient is unable to tolerate oral dosing. For refractory cases, butorphanol (0.2–0.4 mg/kg SQ tid–qid) is very effective. Intravenous fluids are required for patients intolerant of oral hydration methods. Episodes of diarrhea or hematochezia usually require little more than a bland diet as treatment. For cases that last more than one or two days, treatment with loperamide (Imodium A/D, 0.08–0.2 mg/kg, or 2 mg/25 kg PO q8–12hr—caution if using for dogs <10 kg; 0.08 mg/kg PO q12–24hr for cats, with caution) or diphenoxylate (Lomotil, 0.05–1.0 mg/kg PO qid for dogs; 0.063 mg/kg or 0.25 mg/cat PO q8–12hr for cats). Sucralfate (Carafate, 1/4 gm PO q8–12hr) may provide relief from diarrhea in some cats. The diagnosis of sterile hemorrhagic cystitis (SHC) secondary to use of cyclophosphamide is made in the presence of pollakiuria, stranguria, and hematuria with no evidence of UTI. This syndrome is generally observed three to seven days following administration of cyclophosphamide. SHC may occur following the first treatment with cyclophosphamide or following several doses of the drug. SHC is self-limiting but can be severe and a source of great stress to the patient and the client; cases may last as long as

8–10 weeks in my experience, although most resolve within 1–2 weeks. Attempts at treatment of SHC with corticosteroids and NSAIDS have been generally unrewarding despite anecdotal reports of success with antispasmodic agents (such as propantheline). It is recommended that a patient with SHC should not be treated with cyclophosphamide (or related agents) again in the future.

Cumulative or Delayed Toxicity

The classic type of cumulative, delayed toxicity is cardiomyopathy associated with use of doxorubicin. This toxicity is generally avoidable by limiting the lifetime cumulative dose to 180–240 mg/m^2, but even with this precaution, cases of cardiomyopathy may occur. Unfortunately, once cardiomyopathy has developed, it is generally irreversible, and fatal congestive heart failure typically ensues within 6 months. Careful prescreening of patients to rule out preexisting myocardial disease is warranted before using doxorubicin. Blood urea nitrogen, creatinine, and urine specific gravity values should be evaluated in these patients prior to each treatment. Chronic use of alkylating agents such as melphalan and chlorambucil is associated with severe, possibly irreversible myelosuppression, particularly of the platelets. Careful, regular monitoring of trends of peripheral blood cells is vital to prevent such toxicity.

Client Communication

Above all, inform your clients what they may expect and impress upon them the importance of rapid communication with you in the event of *any* complications, no matter how minor. This information will help you preplan any future treatment adjustments as well as prevent minor complications from becoming major ones.

5

Chemotherapy Dosages, Indications, and Adverse Reactions

Asparaginase (Elspar)

Dosage:	10,000 IU/m^2 intramuscularly (IM) every 1–4 weeks.
	400 IU/kg IM every 1–4 weeks.
Indications:	Lymphoma, leukemia.
Adverse Reactions:	Anaphylaxis.

Azothioprine (Immuran)

Dosage:	2 mg/kg orally (PO), once daily for 2 weeks; then 0.5–1.0 mg/kg PO every 48 hours thereafter.

Indications:	Immune suppression (IMHA, IMTP, Evans's syndrome).
Adverse Reactions:	Myelosuppression, nausea.

Bleomycin (Bleoxane)

Dosage:	2 mg/m^2 subcutaneously (SQ) weekly.
Indications:	Carcinomas, lymphoma, leukemias.
Adverse Reactions:	Myelosuppression.

Busulfan (Myleran)

Dosage:	0.2 mg/kg PO daily.
Indications:	Myeloblastic leukemias.
Adverse Reactions:	Myelosuppression.

Carboplatin (Paraplatin)

Dosage:	Dogs—300 mg/m^2 intravenously (IV) every 3–4 weeks. Dogs—90 mg/m^2 IV weekly. Cats—200 mg/m^2 IV every 3–4 weeks.

Indications:	Osteosarcoma, melanoma
Adverse Reactions:	Myelosuppression, vomiting.

CCNU (Lomustine)

Dosage:	60–90 mg/m^2 PO every 3 weeks.
Indications:	Relapsed lymphoma, mast cell tumors, cutaneous lymphoma, mycosis fungoides.
Adverse Reactions:	Myelosuppression, vomiting.

Chlorambucil (Leukeran)

Dosage:	0.2 mg/kg PO daily for 10 days then every 48 hours thereafter.
Indications:	Lymphoma, leukemias, soft tissue malignancies, mast cell tumors.
Adverse Reactions:	Myelosuppression.

Cisplatin (Platinol)

Dosage:	70 mg/m^2 IV every 3–4 weeks or 30 mg/m^2 IV weekly; use a 3- to 4-hour saline diuresis.
Indications:	Osteosarcoma, melanoma.
Adverse Reactions:	Myelosuppression, vomiting, renal failure.

Cyclophosphamide (Cytoxan)

Dosage:	200–350 mg/m^2 PO or IV every 1–3 weeks or 50 mg/m^2 PO daily for 4 days per week.
Indications:	Lymphoma, leukemias, soft tissue malignancies.
Adverse Reactions:	Myelosuppression, hemorrhagic cystitis.

Cyclosporine (Sandimmune)

Dosage:	3–10 mg/kg PO daily.
Indications:	Immune suppression, atopy.
Adverse Reactions:	Vomiting, diarrhea, anorexia.

Cytarabine (Cytosar-U)

Dosage:	100 mg/m^2 SQ TID for 3 days or 10 mg/m^2 SQ q12hr until remission occurs.
Indications:	Leukemias.
Adverse Reactions:	Myelosuppression.

Dacarbazine (DTIC)

Dosage:	200 mg/m^2 IV daily for 5 days.
Indications:	Relapse lymphoma.
Adverse Reactions:	Severe vomiting, myelosuppression.

Doxorubicin (Adriamycin)

Dosage:	>20 lbs = 30 mg/m^2 IV every 2–3 weeks (maximum five times). <20 lbs = 1 mg/kg IV every 2–3 weeks (maximum five times).
Indications:	Lymphoma, soft tissue tumors.
Adverse Reactions:	Myelosuppression, anaphylaxis, vomiting, cardiomyopathy (do not exceed 180 mg/m^2 cumulative administration).

Epirubicin (Pharmorubicin, Ellence)

Dosage:	30 mg/m^2 IV every 2–3 weeks.
Indications:	Lymphoma, soft tissue malignancies, carcinomas.
Adverse Reactions:	Myelosuppression, vomiting, diarrhea, acute hypersensitivity.

Fluorouracil (5-FU)

Dosage:	50 mg/m^2 intralesionally mixed in sesame oil (10 mg/ml final concentration).
Indications:	Soft tissue malignancies.
Adverse Reactions:	Seizures, ataxia.

Gemcitabine (Gemzar)

Dosage:	90–250 mg/m^2 IV every 3 weeks.
Indications:	Pancreatic and hepatocellular carcinomas.
Adverse Reactions:	Myelosuppression, vomiting, anaphylaxis.

Hydroxyurea (Hydrea)

Dosage:	50 mg/kg PO daily until remission.
Indications:	Leukemias.
Adverse Reactions:	Myelosuppression.

Ifosfamide (Ifex)

Dosage:	375 mg/m^2 diluted to 9.75 mg/kg in saline, IV every 2–3 weeks with concurrent MENSA (Mesnex®),

	2-Mercaptoethanesulfonic acid; used to prevent bladder toxicity, such as sterile hemorrhagic cystitis, from ifosfamide or cyclophosphamide metabolites) administration.
Indications:	Soft tissue malignancies, lymphoma, lung tumors.
Adverse Reactions:	Hemorrhagic cystitis (profound), myelosuppression, vomiting.

Melphalan (Alkeran)

Dosage:	0.1 mg/kg PO daily for 10 days then every 48 hours thereafter.
Indications:	Leukemia.
Adverse Reactions:	Myelosuppression.

Methotrexate (Methotrexate)

Dosage:	0.5 mg/kg IV every 3 weeks.
Indications:	Lymphoma, leukemia.
Adverse Reactions:	Myelosuppression, vomiting.

Mitoxantrone (Novantrone)

Dosage:	Dogs—5–6 mg/m^2 IV every 2–3 weeks.

	Cats—5–6.5 mg/m^2 IV every 3–4 weeks.
Indications:	Lymphoma, soft tissue tumors.
Adverse Reactions:	Myelosuppression, anaphylaxis, vomiting.

Paclitaxel (Taxol)

Dosage:	165 mg/kg, diluted to 0.6 mg/ml in 0.9% saline, given as a continuous IV infusion over at least 2 hours every 21 days; 5-day premedication with prednisone, cimetidine, and benadryl required.
Indications:	Lymphoma, soft tissue tumors, mammary tumors.
Adverse Reactions:	Anaphylaxis, vomiting, diarrhea, myelosuppression, alopecia.

Piroxicam (Feldene)

Dosage:	Dogs—0.3 mg/kg PO daily or every 48 hours with or without concurrent antacid administration. Cats—0.3 mg/kg PO every 3–4 days with our without concurrent antacid administration.

Indications:	Transitional cell carcinoma, melanomas, carcinomas.
Adverse Reactions:	Gastrointestinal ulceration.

Prednisone (Prednisone)

Dosage:	40 mg/m^2 PO divided bid, sid, or every 48 hours.
Indications:	Lymphomas, leukemias, insulinomas.
Adverse Reactions:	Polyuria, polydypsia.

Streptozotocin (Zanosar)

Dosage:	500 mg/m^2 IV every 3 weeks with concurrent 3-hour saline diuresis.
Indications:	Insulinomas.
Adverse Reactions:	Nephrotoxicity.

Tamoxifen (Nolvadex)

Dosage:	2.5–10 mg PO bid.
Indications:	Mammary tumors, brain tumors, anticancer drug resistant tumors, melanomas.
Adverse Reactions:	Vaginal discharge, pyometra.

Vinblastine (Velban)

Dosage:	2 mg/m^2 IV slowly every 1–3 weeks.
Indications:	Lymphoma, Leukemias, mast cell tumors, soft tissue tumors.
Adverse Reactions:	Myelosuppression.

Vincristine (Oncovin)

Dosage:	0.5–0.75 mg/m^2 IV every 1–3 weeks.
Indications:	Lymphoma, leukemias, mast cell tumors, soft tissue tumors.
Adverse Reactions:	Myelosuppression.

6

Chemotherapy Dosage Conversion Chart

The following values are derived from the equation $m^2 = 10.0$ (10.1 in cats) $\times$ (weight in grams)$^{2/3}$/10,000. Always confirm all dosage calculations before drug admixing and administration. In the following chart, the first and fourth columns are body weight in kilograms, the second and fifth columns are body weight in pounds, and the third and sixth columns are the calculated value in body surface area (in square meters).

Kg	Lb	m^2	Kg	Lb	m^2
0.5	1.1	0.06	33	72.6	1.03
1	2.2	0.10	34	74.8	1.05
2	4.4	0.15	35	77.0	1.07
3	6.6	0.20	36	79.2	1.09
4	8.8	0.25	37	81.4	1.11
5	11.0	0.29	38	83.6	1.13
6	13.2	0.33	39	85.8	1.15
7	15.4	0.36	40	88.0	1.17
8	17.6	0.40	41	90.2	1.19
9	19.8	0.43	42	92.4	1.21
10	22.0	0.46	43	94.6	1.23
11	24.2	0.49	44	96.8	1.25
12	26.4	0.52	45	99.0	1.26
13	28.6	0.55	46	101.2	1.28
14	30.8	0.58	47	103.4	1.30
15	33.0	0.60	48	105.6	1.32
16	35.2	0.63	49	107.8	1.34
17	37.4	0.66	50	110.0	1.36
18	39.6	0.69	52	112.2	1.41
19	41.8	0.71	54	114.4	1.44
20	44.0	0.74	56	116.6	1.48
21	46.2	0.76	58	118.8	1.51
22	48.4	0.78	60	121.0	1.55
23	50.6	0.81	62	123.2	1.58

(continued)

Kg	Lb	m^2	Kg	Lb	m^2
24	52.8	0.83	64	125.4	1.62
25	55.0	0.85	66	127.6	1.65
26	57.2	0.88	68	129.8	1.68
27	59.4	0.90	70	132.0	1.72
28	61.6	0.92	72	134.2	1.75
29	63.8	0.94	74	136.4	1.78
30	66.0	0.96	76	138.6	1.81
31	68.2	0.99	78	140.8	1.84
32	70.4	1.01	80	143.0	1.88

7

Ten Commonly Used Chemotherapy Protocols

The following protocols are derived from clinical trial results and personal experience with the expectation of achieving an overall remission rate (the sum of all complete and partial responses) of greater than 50% with a 6-month minimum duration of clinical response. Some of these protocols have shown remission rates exceeding 80% and remission durations exceeding 2 years. Remember that most clinical protocols rarely exceed a 20% complication rate and so never truly achieve an expectation consistent with an intent to cure. Increasing the dosage of a drug, shortening the frequency between drug

administrations, or including additional drugs may increase protocol efficacy and clinical toxicity. Please review the section on managing chemotherapy side effects. The concurrent use of radiation therapy may also be indicated. Consult with a local veterinary oncologist and have an open dialogue with the pet owner regarding therapy goals.

Protocol Indications

Protocol 1: Induction protocol for canine osteosarcoma, canine hemangiosarcoma, canine soft tissue carcinomas and adenocarcinomas (thyroid, sweat gland, anal sac). Consider protocol 10 as maintenance therapy for 6–9 additional months. Consider concurrent radiation to the tumor site. Consider mitoxantrone as an alternative to Adriamycin in patients suspect for cardiac disease.

Protocol 2: Induction protocol for canine osteosarcoma, canine bladder tumors. Consider protocol 10 as maintenance therapy for 6–9 additional months. Consider concurrent radiation to the tumor site. Consider mitoxantrone as an alternative to Adriamycin in patients suspect for cardiac disease.

Protocol 3: Induction protocol for canine osteosarcoma, thyroid carcinoma, and lung tumors. Consider protocol 10 as maintenance therapy for 6–9 additional months. Consider concurrent radiation to the tumor site.

Protocol 4: Canine bladder tumors, feline injection-site associated sarcomas (consider concurrent irradiation). Consider protocol 10 as maintenance therapy for 6–9 additional months.

Protocol 5: Canine oral and subungal melanomas (carboplatin is 90 mg/m^2 intravenously [IV] weekly). Tamoxifen may also be indicated.

Protocol 6: Canine and feline lymphoma (continue as scheduled for 18 months).

Protocol 7: Canine and feline lymphoma (continue as scheduled for 18 months). Canine and feline soft tissue tumors (excluding the use of Elspar).

Protocol 8: Canine and feline mast cell tumors (continue as scheduled for 12 months). Consider concurrent radiation therapy for grade III tumors.

Protocol 9: Induction protocol for canine and feline tonsillar squamous cell carcinoma. Consider concurrent radiation therapy.

Protocol 10: Maintenance protocol for various malignancies including canine hemangiosarcoma, canine and feline soft tissue carcinomas and adenocarcinomas, canine and feline lymphoma.

Supportive Drugs Considered Optional to Prevent or Relieve Adverse Reactions

Nausea or Vomiting:	Metoclopramide (Reglan), 0.5 mg/kg orally (PO) every 8 hours for 5 days.
Colitis:	Sulfasalazine (Asulfadine), 33 mg/kg PO every 8 hours for 5 days.
Gastric Ulceration:	Cimetidine (Tagamet), 4 mg/kg PO every 8–12 hours regularly during piroxicam administration.

	Week																								
Protocol	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
1	A*		A		A		A		A																
2	A		CB			A		CB			A		CB												
3	CB			CB			CB			CB			CB												
4	M P	P	P	M P	P	P	M P	P	P	M P	P	P	M P	P	P	P	P	P	P	P	P	P	P	P	P
5	CB	CB	CB	CB	CB	CB	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
6	V E	C		V	C		V E	C		V	C		V E	C		V	C		V E	C		V	C		V E
7	V	C	A		V	C	A		V		C		V		MT		V		C		V		MT		A
8	V L	V L	V L	V L			V L			V L			V L			V L			V L			V L			V L
9	BL	BL	BL	BL	BL																				
10	V		C		V		C		V		C		V		C		V		C		V		C		V

*Drug abbreviations (see text for dosages, administration notes, and adverse effects): A = Adriamycin; CB = carboplatin; M = mitoxantrone; P = piroxicam; V = vincristine; C = Cytoxan; E = Elspar; MT = methotrexate; L = Leukeran; BL = bleomycin.

8

Supportive Care and Rehabilitation

The complications of cancer and chemotherapy are often the most difficult for owners. When treating the veterinary cancer patient, the clinician needs to clearly communicate treatment goals with owners. If animals are apparently made worse by the treatment, owners may be reluctant to continue. Because anorexia, nausea, vomiting, and diarrhea are obvious outward signs, they may be more disturbing than neutropenia, hypercalcemia, lymphadenopathy, or other complications. These signs may also be due to the tumor itself, and distinguishing what is caused by the treatment and what the disease causes may be difficult. Supportive care should be timely and aggressive.

Long-term complications are the chronic or lingering problems after the cessation of therapy, while late effects are delayed problems occurring months to years after treatment. Long-term follow-up will not necessarily eliminate the chronic or delayed effects of therapy, but it will enable pet owners to make better informed decisions about issues affecting the quality of their pets' lives. Awareness of risk can encourage changes in behavior that promote health (e.g., proper diet) and early detection of tumor recurrence (e.g., regular veterinary examinations), thus optimizing the chances for long-term survival.

System-specific or organ damage or failure and premature aging due to chemotherapy, radiation therapy, biologic modifiers, surgery, or any combination of these have been described. Some examples include (1) cardiomyopathy, renal insufficiency, bladder damage, cataracts, muscle atrophy; (2) compromised immune systems causing increased risk of infection (viral, bacterial, or fungal) and possible increased risk of malignancy; (3) damaged endocrine systems leading to thyroid dysfunction, hypothalamic-pituitary dysfunction, or reproductive problems; (4) recurrence and secondary malignant neoplasms; (5) increased risk associated with certain therapies (e.g., bladder cancer as a result of cyclophosphamide therapy).

Other problems associated with cancer therapy may

include (1) functional changes, such as incontinence, immobility due to weakness or orthopedic problems, orthodontic problems, lymphedema, sleep disturbances, pain syndromes, fatigue, or mucosal dryness; (2) cosmetic changes, such as amputations, ostomies, or skin and hair changes; (3) chronic illnesses, such as osteoporosis, arthritis, scleroderma, or hypertension; and (4) psychosocial effects related to physiologic morbidity, such as anxiety, mood changes, or depressed behavior.

Cooperation is required between oncologists, primary care veterinarians, and other veterinary care staff for continued follow-up appropriate to the pet's cancer history. Once cancer therapy begins, emphasis on promotion of health and wellness is necessary, such as nutritional and pain support. Furthermore, everyone involved in the care of the cancer-bearing pet should have a clear understanding regarding the role of cytotoxic agents, radiation therapy, or combinations of both on the incidence and type of long-term complications and late effects of the prescribed cancer treatment plan. Offer appropriate owner education that includes full disclosure of all potential long-term or late complications of treatment, warning signs of possible problems, and symptom management strategies. Promote appropriate behavioral modifications, such as proper nutrition and exercise, to improve and strengthen damaged immune systems and prevent future iatrogenic late effects.

Nutrition

A variety of factors may predispose cancer patients to malnutrition during treatment. Maintenance of an optimal weight and prevention of nutritional deficiencies (and excesses) can improve the patient's outcome. In addition, nutritional modulation may be beneficial in the treatment of the disease. Therefore, nutrition should be an integral part of the management for every cancer patient.

Nutritional Alterations in Cancer Patients

Researchers have shown that a number of metabolic alterations occur in dogs with cancer. Carbohydrate, protein, and lipid metabolism is altered in dogs with a variety of tumors, although the clinical implications and the effect of diet on these alterations are still being investigated. Whether similar metabolic alterations occur in cats with cancer still needs to be determined. Weight loss or cancer cachexia is a very common problem in people with cancer. Unlike simple starvation, in which primarily fat is lost, cancer cachexia involves a loss of both protein and fat. In people, this weight loss is associated with shortened survival and poor quality of life. Two veterinary studies have shown that weight loss is uncommon in oncology patients.[1,2] However, some individuals or even certain patient populations may be more susceptible to weight loss. This might include animals undergoing radiation therapy, since they often undergo prolonged

hospitalization and daily sedation as part of the therapy. A recent study of dogs and cats undergoing radiation therapy showed a median weight loss of 9.4% in dogs and 10.5% in cats. This suggests that preemptive nutritional support may be indicated. When weight loss does occur in the cancer patient, it is important to address this problem. While cancer cachexia is not a common issue in pets, obesity can often be a problem in dogs undergoing chemotherapy. This may be the result of prednisone use as part of the chemotherapy protocol or from owners who indulge their sick pet. In some of these patients, obesity can be severe enough to interfere with the patient's quality of life (e.g., reduced mobility, musculoskeletal disorders). Early discussion of the problems of obesity with owners is recommended when weight gain is first noted, not after it is too late. It is extremely difficult to convince an owner of a cancer patient to put their pet on a strict reduction diet.

Nutritional Assessment of the Cancer Patient

A careful diet history can help identify the presence and significance of the following factors that put patients at risk of malnutrition (e.g., weight loss, changes in appetite) or overnutrition (e.g., obesity, vitamin or mineral excesses from supplementation). Sometimes, a careful diet history reveals an inappropriate diet, excessive supplementation, or other nutritional problems. Monitoring body weight and body condition throughout

therapy for cancer patients is critical. Trends in body weight can identify weight gain or loss before it becomes a problem. Body condition scoring provides additional information on whether the body weight is appropriate for that animal (e.g., a 1–9 scale with 5 = optimal body condition). Other physical examination findings may indicate the presence of malnutrition (e.g., muscle loss, poor hair coat, poor wound healing), although these signs are not usually seen until a relatively advanced stage of malnutrition. It is much better to identify an animal at risk for malnutrition (e.g., frequent anesthesia, reduced appetite) and *prevent* malnutrition from occurring than try to correct it. It is important to ask owners specifically about nutritional supplement use in dogs and cats with cancer. A large percentage of owners whose pets have cancer are administering nutritional or herbal supplements, and they may not voluntarily provide this information unless specifically asked. Ask both what types of supplements are given and the doses. This information can help determine whether the supplement use and the dose are appropriate and whether any drug-nutrient interactions might occur with other forms of therapy being used.

Anorexia

Many patients undergoing chemotherapy or radiation therapy develop anorexia at some time during the course of the treatment. Anorexia can have direct detri-

mental effects because it can lead to weight loss. In addition, anorexia is a common contributing factor to an owner's decision for euthanasia. Appetite stimulation with cyproheptadine or benzodiazepine derivatives is not usually very effective but sometimes may help to give an animal a "jump-start" back into eating. Dietary changes can be helpful for anorexic animals. Switching to a more palatable food may enhance food intake (changing from dry to canned, from canned to dry, or to a different brand of food). Palatability enhancers also can improve appetite (e.g., low-salt tomato sauce, honey, yogurt for dogs; tuna juice, cooked meat for cats). Fish oil supplementation, which is high in n-3 fatty acids, also may reduce anorexia in some animals. The method of feeding may influence eating behavior. A recent study showed that food intake of hospitalized animals improved significantly when they were hand-fed compared to voluntary eating. If the pet will not eat enough by mouth, however, nutrition support is indicated.

Enteral Nutrition

When animals will not eat sufficient food voluntarily, nutrition support techniques are necessary to ensure adequate nutrient intake. Enteral nutrition is the preferred method for nutrition support. Enteral nutrition is safer, more physiologic, and less expensive than parenteral nutrition and helps maintain gastrointestinal (GI) structure and function. Enteral nutrition should be

used in any patient that will not or cannot voluntarily eat adequate calories orally. Contraindications include vomiting, severe malabsorption, and an inability to guard the airway. A nasoesophageal tube can be used for short-term nutrition support (3–4 days), while esophagostomy or gastrostomy tubes are indicated for long-term management. An esophagostomy or gastrostomy tube can often be coordinated with sedation for other procedures (e.g., diagnostic procedures, surgery, or, anesthesia for radiation). Diets for tubes depend on the patient and type of tube being used. Nasoesophageal tubes require a liquid diet, while esophagostomy and gastrostomy tubes are large enough to use either a blenderized pet food or a "critical care" diet (e.g., Hill's a/d, Topeka, KS; Eukanuba Maximum Calorie, Dayton, OH). Human enteral diets are used by some practices, but these are unbalanced for dogs and cats without supplementation. In cases where human enteral diets are preferred, supplementation with protein and B vitamins (for dogs and cats), plus taurine and arginine for cats is required to avoid deficiencies. Although other nutrients in these formulas also do not meet canine and feline requirements, they usually cause no problem with short-term use. Other nutrients, such as glutamine, arginine, n-3 polyunsaturated fatty acids, and micronutrients may have pharmacological benefits above and beyond their nutritional requirements, especially in the cancer patient.

Parenteral Nutrition

If the entire GI tract is nonfunctional or conditions prohibit the use of enteral nutrition, the other option is to feed parenterally. Parenteral nutrition can be delivered by a central vein (total parenteral nutrition, or TPN) or a peripheral vein (peripheral or partial parenteral nutrition, or PPN). Although PPN is no replacement for TPN, it can be useful for short-term nutritional support (<5 days) in a nondebilitated animal to help prevent malnutrition. It also can be used to supplement tube feeding in some cases. Since PPN can be formulated to meet only 50–75% of a patient's energy requirements, it should not be used in a debilitated patient. Another temporary option for PPN is commercial mixes containing a protein and carbohydrate source (e.g., Procalamine, McGaw, Irvine, CA; Quick Mix, Clintec, Deerfield, IL). Although these solutions only provide approximately 25% of energy requirements when administered at maintenance fluid rates, they can be useful as an interim or short-term source for parenteral nutrition. Like TPN, PPN has potential complications, including metabolic disorders, mechanical complications, and sepsis; so careful handling of catheters, lines, and solutions is required. Monitoring for metabolic abnormalities is necessary to prevent complications from all forms of parenteral nutrition.

Patient Assessment and Nutritional Needs

The veterinary community is beginning to appreciate the relationship between enteral nutritional support and proper medical and surgical management of companion animals. The optimal route for meeting the nutritional requirements of companion animals is the gastrointestinal tract. Enteral nutritional support uses some part of the gastrointestinal tract to feed the patient that cannot or will not eat but can digest and absorb nutrients. Enteral feeding is the simplest, fastest, safest, and least expensive method of feeding companion animals that require nutritional support. Assessment of the patient requiring enteral nutritional support should include an assessment of the animal, the current diet, and feeding management. The combined subjective and objective data collected can be used to formulate an appropriate enteral feeding plan and define the specific nutritional goals to manage the patient. The feeding plan then must be implemented and monitored; and if the animal goes home with an enteral tube, the client must be educated. Frequently the veterinarian must rely on clinical judgment rather than objective data to decide to institute enteral nutritional support. However, simple tools such as a thorough clinical assessment are surprisingly sensitive. The primary goal of nutritional assessment is to predict the animal that can benefit from nutritional support. In the future, other techniques may be available clinically to provide a more objective and quantitative

assessment of nutritional status. Anorexia and malnutrition, particularly protein calorie deficiency, is common in companion animals requiring nutritional support. Malnutrition reduces synthesis of plasma proteins, impairs wound healing, and decreases the immune response. It is essential for the veterinarian to assess the nutritional status of the patient on initial presentation and reassess the animal at appropriate intervals after nutritional intervention to determine whether a change in nutritional status has occurred.

PATIENT ASSESSMENT Nutritional assessment of the companion animal is a structured process that includes review of the signalment, history, and medical record; physical examination; laboratory evaluation; and estimation of nutritional requirements based on physiological state. Review of the signalment, history, and medical record should include questions related to changes in body weight, food intake, and drugs and other therapies that may affect appetite or nutrient metabolism. The medical record may yield important objective information that may provide clues to the animal's nutritional status. Several drug-nutrient interactions may influence dietary intake or nutritional requirements. For example, animals receiving diuretics may have increased needs for potassium, magnesium, and calcium. The patient's physiological state should be determined by collecting information related to body weight, body condition score, growth rate, reproductive status, species, and the nature

and duration of the presenting illness. These parameters affect the nutrient requirements of the animal for a given nutrient. Furthermore, the client should be questioned about environmental factors, such as activity and housing, which could also alter nutrient requirements. The client should also be questioned about the animal's dietary history, including the current diet, eating habits, and feeding management. The dietary history should strive to identify all items of food being consumed by the animal, including table scraps, treats, and supplements. The amount of each food offered and consumed should be specified and factors that could affect intake, such as other animals in the household, should be recorded. Companion animals that have been anorexic or had restricted food intake for longer than 3 days may benefit from nutritional intervention.

Physical examination can help determine the nutritional status of companion animals. Body weight and body condition score (score of 1 to 5, with 1 being thin and 5 being obese) provide a subjective estimation of the animal's body composition. Fat cover over the ribs, down the topline, around the tailhead, and ventrally along the abdomen should be evaluated. A body condition score can be combined with zoometric measurements, such as pelvic circumference, to provide a better estimate of body fat. Body weight can be compared to usual or optimum body weight and breed standards. Nutritional support is indicated if the patient recently lost more than 10% of its

usual or optimum body weight. The patient's general appearance should be assessed, including the presence or absence of edema, ascites, and nonhealing wounds. Evaluation of hair coat, skin, and nails may provide an indication of malnutrition. Growth retardation, muscle weakness, or atrophy aids in the identification of catabolic, critically ill patients. Dysfunction of organs, such as the liver, heart, kidneys, or lungs, may explain poor body weight and condition and help determine the most appropriate nutrient profile for the enteral diet. Laboratory evaluations may serve as objective indicators of nutritional status; however, no single laboratory parameter analyzed routinely in veterinary medicine can accurately assess nutritional status. Laboratory tests, such as those for albumin, lymphocyte count, pack cell volume, and total protein, may provide insight into the patient's nutritional status. For example, hypoalbuminemia may indicate visceral protein depletion due to chronic undernutrition or protein loss. In humans, hypoalbuminemia correlates with increased morbidity and mortality rates and longer hospital stays. In the future, shorter half-life serum proteins, such as prealbumin, transferrin, retinol-binding protein, or fibronectin, may be available to assess short-term changes in nutritional status. Serum glucose is important to assess in severely stressed, catabolic patients. Furthermore, since malnutrition affects the immune status of the patient, perhaps, in the future, an immune profile could be developed to provide a more sensitive

assessment of nutritional status. Serum biochemical profile changes associated with major organ dysfunction may provide indications of problems that may be nutrient sensitive and therefore affect the selection of the enteral diet. For example, if the patient requiring enteral nutritional support has associated renal or liver disease, diet selection would dictate a modification in the levels of certain nutrients. Other laboratory tests that may be of value in nutritional assessment include urinalysis and fecal analysis.

NUTRITIONAL NEEDS The patient's nutrient and water requirements should be calculated and compared with the nutrient and water intake of the animal. Nutrient intake can be estimated from the dietary history or be monitored and evaluated if the animal is hospitalized. In most cases, the animal requiring enteral nutritional support has an intake that is less than its requirements. Calculation of the nutrient requirements of the patient requiring enteral nutritional support depends on the physiologic state of the animal. Many of these animals are critically ill, at least initially, and may have suffered traumatic injury, sepsis, or major organ disease in combination with food deprivation. Many conditions commonly diagnosed in veterinary medicine increases the animal's risk of malnutrition. Disorders that may be associated with increased losses of protein and electrolytes include vomiting, draining wounds, ileus, diarrhea,

abscesses, chylothorax, enteropathy or nephropathy, and malassimilation. Conditions that may be associated with increases or decreases in nutrient requirements include blood loss, liver disease, renal disease, trauma, sepsis, pulmonary disease, and cancer. Nutritional support may be indicated in animals receiving antinutrients or catabolic drugs that result in anorexia or dysphagia. Cats have special nutritional requirements, as compared to dogs, because they are strict carnivores. These special dietary requirements of the cat should be considered when considering the selection of an enteral product. Among the special physiologic and metabolic requirements of cats are more protein than needed by dogs, an essential need for taurine, a requirement for arachidonic acid in their diet, more niacin and pyridoxine, and taking into account the feline inability to convert B-9 carotene to vitamin A. These differences become important when selecting an enteral product to feed a cat. Human liquid diets are not balanced for cats, and many of the products lack sufficient taurine.

The following steps should be used to calculate the nutrient requirements of the patient (both dog and cat) and the feeding level for enteral nutritional support:

1. *Calculate resting energy requirement.* The resting energy requirement (RER) is the amount of energy required by the animal in a postabsorptive resting state and accounts for a thermoneutral environment and

physiological influences. In human medicine, RER is determined by indirect calorimetry, but this technique is not widely used in veterinary medicine. In critically ill companion animals, the goal is to meet resting energy requirement on a daily basis. Critically ill animals are hospitalized, confined to a cage, and have energy requirements below maintenance levels. Many times patients have not eaten for several days and therefore should be adapted to the enteral diet over several days. The resting energy requirement is the starting point in meeting daily energy requirements. If the animal tolerates this level of feeding, then energy intake can be increased over time. Patients sent home and fed long term through feeding tubes are fed at higher levels, closer to maintenance levels. Again, the goals for energy intake are dictated by physiological state of the animal. In many of the enteral diets fed to dogs and cats, the nutrient content is balanced to the caloric content of the diet. Therefore, if you feed to meet the calculated daily energy requirement of the patient, all other nutrient requirements are met. Water should be provided at the rate of 1 ml for each kcal of calculated daily energy requirement.

2. *Select an enteral diet.* Diet selection for enteral nutritional support depends on tube size and location, product availability and cost, functioning of the gastrointestinal tract, and the experience of the veterinarian. Products available to feed include blended pet foods, veterinary-formulated critical care diets, and human

liquid enteral diets. Pet foods are higher in protein and fat than commercially available human liquid diets, have various nutrient profiles, are readily available, and are the least expensive products to feed for the enteral support of dogs and cats. Both blended pet foods and veterinary-formulated critical care diets cause fewer complications, such as diarrhea, and usually require fewer feedings per day than human enteral diets. In most cases, a high energy and protein food should be chosen as the enteral diet. However, if the patient has renal or liver disease, a veterinary therapeutic diet can be blended and fed through the tube. Patients fed veterinary diets through the feeding tube may be fed the food directly when they have regained their appetite, thereby eliminating a diet change. The veterinary-formulated critical care diets have increased levels of protein and fat as compared to average maintenance foods to aid in sparing lean body mass and maintain host defenses. These diets may have increased levels of branched chain amino acids, n-3 fatty acids, B-9 complex vitamins, antioxidants such as vitamin E, glutamine, arginine and selected minerals (e.g., potassium, magnesium, and zinc). These diets may be formulated to be fed to both dogs and cats. Such diets are contraindicated in animals with renal or liver disease or for animals with gastrointestinal problems that have resulted in fat intolerance. Human liquid enteral diets may cause diarrhea when fed to companion animals, and the diets are usually more expensive. Furthermore, the human liquid enteral diets

are not balanced for cats and must be modified with nutrient modules. Human liquid diets are available in polymeric and monomeric formulations. Monomeric or elemental diets contain nutrients in their simplest form and require minimal digestion by the patient. Polymeric, or meal replacement, diets contain mixtures of proteins, fats, and carbohydrates from simple ingredients. Polymeric diets require normal digestion. Human liquid enteral diets have the advantage that they can be fed through small feeding tubes and are available in a wide variety of nutrient profiles.

3. *Determine food dosage.* Calculate the total food dose (ml), daily energy requirement (kcal), and energy density of the product (kcal/ml). Initiate feeding by dividing the total daily amount to be fed by the number of feedings per day. Begin by feeding one third of the food per day and gradually increase the amount of the enteral diet per day. For example, a feeding schedule for the first three days would be the following: calculated diet + two thirds of the water on day 1, calculated diet + one third of the water on day 2, full calculated diet with no water added on day 3.

4. *Determine feeding frequency.* Frequency of feeding depends on the diet type, route of feeding (tube type), and digestive and absorptive capacity of the patient. For example, an animal fed through an enterostomy tube may require constant infusion of the diet.

5. *Reassess.* Reassess the patient to determine its response to the diet and modify the feeding plan if needed.

Pain Management

Management of pain constitutes an integral part of successful treatment for a wide variety of human diseases. This is particularly true for patients with malignancies, where the physiologic and psychological effects of pain may have a great impact. While advances in the understanding and treatment of pain in animals have lagged some years behind similar progress in the human field, it is now widely and increasingly accepted that appropriate therapy for pain must accompany primary treatment of many animal diseases, including cancer.

Incidence

Approximately 50–80% of human patients with advanced cancer experience pain during the course of their disease. The majority of these patients do not obtain satisfactory relief. This constitutes a major problem in the medical field, because unrelieved pain can significantly diminish the patient's quality of life. Among the factors that may contribute to inadequate pain management are the overriding fears of addiction, health care professionals' lack of knowledge about pain medication and new

pharmacological interventions, and lack of confidence in the efficacy of behavior techniques. Similar factors exist in the veterinary medical community and are not limited in application to pets with cancer.

Cancer pain can be acute or chronic. Acute pain generally results from tissue damage and is of limited duration. The physiological effects (e.g., tachycardia) observed result from stimulation of the autonomic nervous system. Once the cause of pain has been identified, it can be successfully treated and is often completely eradicated. Chronic pain, on the other hand, is persistent, usually longer than 3 months in duration. Because the pathology or cause of the pain cannot be altered, the nervous system eventually adapts and ceases to be hyperactive; the pain may then manifest itself as depression or anxiety.

Causes

The severity and prevalence of pain that cancer pets experience depends on many factors, including the site and stage of the disease and the location of metastases. Cancer-related pain can result from the disease process or cancer therapy. The most common causes of pain from direct tumor involvement are metastatic bone disease, nerve compression or infiltration, and hollow viscus (e.g., bowel) involvement resulting in obstruction. All the

major treatment modalities may cause pain syndromes. Additionally, pets may have preexisting chronic pain unassociated with either the disease or its treatment.

Pain affects each pet differently, depending on factors such as age, perception, pain threshold, and past experiences with pain. Insomnia, fatigue, and anxiety can lower the pain threshold; while rest, sleep, and diversion can raise it.

Pain Assessment

An accurate assessment of the pet's pain experience provides a basis for an evaluation of various pain management techniques. A comprehensive assessment includes information about the following dimensions of pain: location, intensity, factors influencing its occurrence, observed behavior during pain, psychosocial variables (i.e., attitudes, situational factors), effects of pain, effects of therapy, and patterns of coping. A variety of pain assessment tools have been developed for use in humans, ranging from simple self-reports about pain intensity to detailed descriptive information. In veterinary medicine, assessment of chronic pain may be enhanced through the pet owner's use of a pain diary, in which descriptions of the characteristics of the pain and the effectiveness of management techniques can be recorded.

Treatment for Pain

The goal of pain management is not only relief from pain but also the maintenance of the pet's normal quality of life. All methods of pain management attempt to either control the cause of the pain or alter the pet's perception of it.

Although pain management techniques are many and varied, therapeutic approaches can be classified as either pharmacologic or nonpharmacologic. Pharmacologic pain control involves the use of analgesics as well as other medications that potentiate the analgesic's effects or modify the pet's mood or pain perception. Nonpharmacologic approaches include behavioral techniques, radiation, surgery, neurological and neurosurgical interventions, and traditional nursing and psychosocial interventions; the latter measures attempting to promote comfort and evaluate the effectiveness of the therapy. Because of the complex nature of cancer-related pain, successful management usually involves a combination of techniques.

Cancer pain management in the geriatric pet calls for special considerations. Aging pets are at an increased risk of drug reactions, because drug adsorption, distribution, metabolism, and elimination change with age, disease status, and medication interactions.

PHARMACOLOGIC MANAGEMENT Veterinary care personnel must aggressively manage acute pain in the

cancer pet with medication to return the pet to a pain-free state as soon as possible. Once the pain is relieved, the pain medication is decreased to the lowest dosage or mildest analgesic that maintains the pain-free state. When the pain cycle is broken, pets can be sustained on minimal amounts of pain information.

Chronic pain, however, requires very different medication management. For example, a pet with chronic pain is usually started on a nonnarcotic analgesic and moves to a narcotic as more effective pain control is needed.

The World Health Organization (1987) states that "analgesic drugs are the mainstay of cancer pain management" and advocates a three-step "analgesic ladder" for decision making. This schema is appropriate for use in veterinary medicine. Step 1 includes the use of a nonopiod drug with or without an adjuvant drug (e.g., aspirin + carprofen + misoprostil). If pain persists or increases, pain management moves to step 2, a weak opioid plus a nonopioid, with or without an adjuvant drug (e.g., acetaminophen + codeine with or without carbamazepine). If pain persists or increases, pain management moves to step 3, a strong opioid, with or without a nonopioid, with or without an adjuvant drug (e.g., morphine with or without acetaminophen with or without dexamethasone).

Nonnarcotic pain agents are best used for mild cancer pain. This category includes aspirin, acetaminophen,

and nonsteroidal anti-inflammatory drugs (NSAIDs). Nonnarcotic agents may also be used to potentiate the effect of narcotic analgesics in pets with severe pain. However, these agents have a ceiling effect: Increasing the dosage beyond a certain point produces no additional pain relief. NSAIDs reduce the production of prostaglandin by inhibiting cyclooxygenase (COX). Their analgesic properties are due primarily to their anti-inflammatory effects. Common side effects of these compounds include gastrointestinal and renal toxicity. The newer agents in this class include carprofen and etodolac. These compounds have a favorable COX1:COX2, which in theory reduces the possible side effects associated with this class. Piroxicam is also included in this class. Other NSAIDs that may be useful in the small animal patient include ketoprofen and ketorolac.

Narcotic analgesics (opioids) are used for the treatment of moderate to severe cancer pain. They are categorized as either narcotic agonist or narcotic agonist-antagonist drugs. This is the largest and perhaps most valuable class of analgesic agents. These agents interact with specific receptors in the brain and spinal cord and are very efficacious. The side effects associated with this class are usually minimal, with respiratory depression, bradycardia, and hypotension being of most concern. Using opiate antagonists can alleviate life-threatening side effects. The opioid agents most commonly used include morphine, butorphanol, fentanyl,

and buprenorphine. Innovative modes for administration include continuous rate infusion, epidural administration, and the transdermal fentanyl delivery system (patch).

One model explaining the actions and effects of the opioids, the multiple opioid receptor theory, proposes that narcotic agonist drugs, such as morphine and codeine, bind with specific opiate receptor sites. A drug can bind to three kinds of receptor sites, or portions of the nerve cell: the μ (mu) receptor associated with analgesia and respiratory depression, the κ (kappa) receptor with sedative effects, and the σ (sigma) receptor with psychomimetic effects.

Although the multiple opioid receptor theory is still evolving and does not yet completely explain narcotic analgesia, pure narcotic agonists such as morphine and codeine are thought to occupy the μ receptor without antagonizing activity at the other receptor sites. Narcotic agonists-antagonists occupy the κ receptor for pain relief, also antagonizing the effects of pure agonists at the μ receptor. Three agonist-antagonists are butorphanol, nalbuphine, and pentazocine.

Adjuvant analgesic drugs are also used to treat cancer pain. This group includes amphetamines, anticonvulsant agents, phenothiazines, tricyclic antidepressants, steroids, antihistamines, and levodopa. Although their exact mechanisms of action for pain relief are not well understood, these drugs relieve pain when used alone or in combination with other nonnarcotics or narcotics.

Pain medication may be given by the following routes: orally, rectally, subcutaneously, intramuscularly, intravenously, intrathecally, and epidurally. Conditions such as thrombocytopenia, neutropenia, and duration of a medication's effect must be taken into account when selecting the route. The peak of a drug's effect depends largely on the route of administration. Oral medications usually peak in 2 hours, intramuscular drugs in 1 hour, and intravenous drugs in 15–30 minutes. The duration of effect varies widely and should be carefully considered.

The schedule for administering analgesics appears to be an important factor in their effectiveness. Research shows that around-the-clock (ATC) rather than as needed (PRN) administration of analgesics is more effective in the control of chronic pain. In many cases, doses of analgesics may be decreased with ATC scheduling, because the pain intensity is consistently less.

Pets with cancer may be undermedicated for their pain because veterinary care personnel believe that cancer-bearing pets usually develop a tolerance to the effects of opioids rather than an addiction. Tolerance to narcotics can occur at any time and requires increasing doses to produce the same level of analgesia. Pets also develop tolerance to the serious side effects of narcotics (e.g., sedation, respiratory depression) at the same rate as tolerance to analgesia, so they can accept larger doses of narcotics without overdosing.

Analgesics and Dosages Available for Use in Dogs and Cats

Narcotic Analgesics in Dogs	**Nonsteroidal Anti-Inflammatory Drugs in Dogs**
Morphine, 0.25–5.0 mg/kg IM or SQ every 4 hours	Aspirin, 10–25 mg/kg PO every 8 hours
Oxymorphone, 0.2 mg/kg IM, SQ, or IV every 6 hours	Phenylbutazone, 10–25 mg/kg PO every 8–12 hours
Butorphanol, 0.4–0.6 mg/kg PO, IM, SQ, or IV every 4–8 hours	Carprofen, 1mg/lb PO every 24 hours
	Piroxicam, 0.3 mg/kg PO every 24 hours
Narcotic Analgesics in Cats	**Nonsteroidal Anti-Inflammatory Drugs in Cats**
Morphine, 0.1 mg/kg IM, SQ, or IV every 4 hours	Aspirin, 10–20 mg/kg PO every 48–72 hours
Oxymorphone, 2–4 mg/kg IM every 2 hours	Piroxicam, 0.3 mg/kg PO every 72 hours
Butorphanol, 0.4–0.8 mg/kg PO, IM, or IV every 3–8 hours	

IM, intramuscularly; SQ, subcutaneously; PO, orally; IV, intravenously.

Like insulin, pain medications can be administered on a continuous basis into subcutaneous tissue through a small-gauge butterfly needle taped in place. Narcotics

can also be continuously infused epidurally or intrathecally with the placement of an indwelling intrathecal catheter. This technique is associated with fewer central nervous system effects than systemic administration of narcotics. The major problem observed with intraspinal delivery of narcotics is respiratory depression.

Fentanyl patches are labeled for managing chronic cancer pain in humans, specifically people who cannot tolerate oral medications. The efficacy and convenience of this delivery system have generated interest in the use of this treatment for postoperative pain in both human and veterinary medicine. Fentanyl is not approved for use as a single agent in dogs and cats. The patch consists of a gel matrix containing fentanyl, a lipid-soluble opiod that diffuses through the skin and achieves blood concentrations high enough to produce analgesia. A variety of sizes deliver 25, 50, 75, and 100 mg/hr, with the delivery rate a function of the surface area of the patch. Patches are designed to provide continual release for about 72 hours. In dogs, there appears to be a 6- to 12-hour latency to achieve plasma concentrations associated with analgesia and up to 24 hours for plasma concentrations to reach a plateau. The principal advantage of fentanyl patches is provision of hands-off analgesia. One disadvantage is body temperature; fever or other causes of elevated body temperature (laying on a heating pad) can increase drug delivery substantially. To circumvent this, many apply the patch to the dorsal neck,

secured with a light wrap. For cats and small dogs, a 25 mg patch is used. For medium-sized dogs (5–20 kg), a 50 mg patch is used. Larger dogs (20–30 kg) may require a 75 mg patch; and giant dogs (>30 kg) may require the 100 mg patch. Side effects may include euphoria (in cats) and increased appetite. Deleterious side effects may include agitation, dementia, heightened response to the environment, and mild sedation or ataxia. However, side effects, when used properly, are uncommon.

NONPHARMACOLOGIC MANAGEMENT Nonpharmacologic pain management approaches include surgery, radiation, neurological and neurosurgical interventions, behavioral techniques, and nursing interventions. Both radiation therapy and surgery may be used for cancer pets with enlarging tumors or advanced disease to decrease the tumor mass and reduce painful compression of adjacent structures. These procedures are conducted for palliative purposes only.

Neurosurgical interventions are generally reserved for pets that cannot obtain adequate relief with analgesics, palliative radiotherapy, or surgery. Most neurosurgical procedures involve interruption or destruction of the pain pathway at some point along the route to the brain or in the brain itself. The risks and benefits of these techniques must be discussed thoroughly with pet owners, because in many cases, the pet will have residual motor or sensory deficits.

Neurostimulation techniques are based on the gate-control theory of pain. Some research indicates the pathways in the spinal cord can accommodate only a certain amount of stimulation before sensory overload occurs. With neurostimulation, competitive nonpainful (e.g., vibratory) impulses are used to block the transmission of painful impulses along nerve pathways. Neurostimulation can be applied transcutaneously, as occurs with transcutaneous electrical nerve stimulation (TENS), or via surgically implanted electrodes in the spinal cord.

Behavioral techniques such as relaxation, distraction, biofeedback, imagery, and hypnosis are now widely used to manage cancer-related pain in people. In general, behavioral techniques are designed to alter the response to pain by fostering a deep relaxation and a shifting of attention to something other than the pain. These approaches, although controversial and likely ineffective for use on most pets, should be used in combination with and not as a substitute for appropriate medication. Care must be taken not to misinterpret the efficacy of these techniques as an indication that the pet is not really experiencing pain.

Oral Complications

Etiology

Identification of high-risk patients enables the veterinary care providers to initiate pretreatment evaluation and

recommend prophylactic measures to minimize the incidence and morbidity associated with oral toxicity. The most significant risk factors for the development of oral complications during and following treatment are preexisting oral or dental disease, inadequate oral care during therapy, and any factors that may compromise the integrity of the oral mucosa. Additional risk factors (not ranked in order) include the type of malignancy (involved sites and histology); the antineoplastic agents used, the dose, and the administration schedule; the radiation field, the dose, and the administration schedule; severity and duration of anticipated myelosuppression; and patient age. Preexisting oral conditions, such as dental calculus, broken teeth, faulty restorations, periodontal disease, gingivitis, and prosthodontic appliances, contribute to the development of local infections and may serve as a focus for systemic infections. Bacterial and fungal colonization of dental calculus, plaque, dental pulp, periodontal pockets, operculum defects, dentures, and dental appliances constitute a reservoir of pathogenic and opportunistic organisms that may develop into local or systemic infections during episodes of immune suppression or neutropenia. Other sources of irritation may exacerbate mucosal thinning and atrophy, producing local ulceration (stomatitis).

CHEMOTHERAPY-INDUCED COMPLICATIONS Because gastrointestinal epithelial cells have a cell turnover rate

similar to leukocytes, the period of greatest damage to the oral mucosa frequently correlates with the white blood cell nadir. Resolution of oral toxicity generally coincides with granulocyte recovery. The lips, tongue, floor of the mouth, buccal mucosa, and soft palate are more severely affected by drug toxicity than the hard palate and gingiva; this may be due to their faster rate of epithelial cell turnover. The role of vascularity in stomatitis may be inferred from the effect of topical cryotherapy in preventing or lessening mucositis from agents such as fluorouracil (5-FU). The antineoplastic agents most likely to cause mucositis include bleomycin, doxorubicin, 5-FU, methotrexate, vinblastine, and vincristine. The risk is exacerbated when chemotherapeutic agents that typically produce mucosal toxicity are given in high doses, in frequent repetitive schedules, or in combination with ionizing irradiation (e.g., conditioning regimens prior to bone marrow transplant).

RADIATION-INDUCED COMPLICATIONS Local irradiation to the head and neck region not only can cause the specific histologic and physiologic changes of the oral mucosa caused by cytotoxic therapy but also structural and functional alterations of underlying supportive tissues, including salivary glands and bone. High-dose radiation to tooth-bearing bone causes hypoxia, reduction in vascular supply to the bone, and tissue breakdown leading to bone exposure, infection, and necrosis. Both ionizing radiation to the head and neck regions and

antineoplastic agents impair cell division, disrupting normal replacement of the oral mucosa. Radiation damage, however, is anatomically site specific. It depends on the amount and kind of radiation used, total dose administered, and field size and fractionation. Radiation-induced damage also differs from that induced by chemotherapy in that tissue volumes treated with radiation continue to remain in jeopardy throughout the life of the patient; they are more easily damaged by subsequent toxic drug or radiation exposures, and normal physiologic repair mechanisms are compromised as a result of permanent cellular depopulation.

SURGERY-INDUCED COMPLICATIONS In patients with osteoradionecrosis involving the mandible or facial bones, surgical debridement may be disfiguring, and reconstruction efforts may be futile unless tissue oxygenation is improved prior to surgery. Hyperbaric oxygen therapy has been shown to stimulate new capillary formation (angiogenesis) in affected tissues and is being used as an adjunct to surgical debridement in humans.

Prevention

The incidence of oral complications in patients who do not have head and neck malignancies can be reduced significantly when an aggressive approach to oral care is initiated prior to treatment. Primary preventive measures, such as well-balanced nutritional intake, adequate

oral hygiene, and early detection of oral problems, are important pretreatment interventions. A veterinary care provider familiar with the oral complications of cancer treatment should examine the patient prior to treatment (with chemotherapy as well as with radiation therapy to the head and neck). Ideally, this examination is performed 2–4 weeks prior to treatment to permit adequate healing of any required dental procedures. The examination allows the veterinarian to determine the condition of the oral mucosa and supportive structures prior to therapy and to initiate necessary interventions that may reduce oral complications during and after therapy. A program of oral hygiene should be initiated, and the pet owner should be instructed about the importance of good oral hygiene prior to initiating treatment.

Specific Oral Complications

MUCOSITIS AND STOMATITIS The terms *mucositis* and *stomatitis* are often used interchangeably but may include some general distinctions. *Mucositis* describes a toxic inflammatory reaction affecting the gastrointestinal (GI) tract from mouth to anus, which may result from exposure to chemotherapeutic agents or ionizing radiation. Mucositis typically manifests as an erythematous, a burn-like lesion, or as random, focal-to-diffuse ulcerative lesions. It may be exacerbated by local factors. *Stomatitis* refers to any inflammatory reaction affecting the oral mucosa, with or without ulceration, and may be caused

or intensified by local factors. Stomatitis can range from mild to severe; the patient with severe stomatitis is unable to take anything by mouth. In common practical usage, however, *mucositis* and *stomatitis* are used indiscriminately to describe the same phenomena. Erythematous mucositis may appear as early as 3 days after exposure to chemotherapy but more typically within 5–7 days. Progression to ulcerative mucositis typically occurs within 7 days after the start of chemotherapy. Veterinary care providers should be alert to the potential for increased toxicity with escalating dose or treatment duration in clinical trials that demonstrate GI (mucosal) toxicity. Combination or high-dose chemotherapy may produce severe mucositis. Drugs administered by continuous infusion or on frequent, repetitive, intermittent schedules (e.g., vincristine) are more likely to cause mucositis than equivalent amounts of the same drugs given in a single bolus. Mucositis is self-limiting when not complicated by infection and typically heals completely within 2–4 weeks. Systematic assessment of the oral cavity following treatment permits early identification of toxicity and initiation of oral hygiene measures designed to prevent or decrease further complications. Once mucositis has developed, its severity and the patient's hematologic status guide appropriate oral management. Meticulous oral hygiene and palliation of symptoms become the focus of care. In the absence of controlled clinical trials, many of the management recommendations are anecdotal.

INFECTION Oral mucositis can be complicated by infection in the immunocompromised patient. Not only can the mouth itself become infected, but the loss of the oral epithelium as a protective barrier results in local infections and provides a port of entry for microorganisms into the systemic circulation. Once mucosal integrity is affected, indigenous oral flora, as well as nosocomial and opportunistic organisms can cause local and systemic infections. As the absolute neutrophil count falls below $1{,}000/mm^3$, the incidence and severity of infection rise. Patients with prolonged neutropenia are at higher risk for the development of serious infectious complications. Nonpharmacologic approaches to preventing infection and prophylaxis with antimicrobials are being evaluated in controlled trials. Antibiotics used during prolonged neutropenia alter oral flora, creating a favorable environment for fungal overgrowth that may be exacerbated by concurrent steroid therapy. The majority of oral bacterial infections are gram-negative due to the shift in the colonization of the oral cavity from predominantly gram-positive to enteric gram-negative organisms.

HEMORRHAGE Hemorrhage may occur during treatment-induced thrombocytopenia or coagulopathy. Sites of underlying periodontal disease may bleed spontaneously or from minimal trauma. Oral bleeding may be minimal, with petechiae located on the lips, soft palate, or floor of the mouth, or it may be severe, with oral hemorrhage, especially in the gingival crevices. Spontaneous

gingival oozing may occur when platelet counts diminish to less than $50{,}000/mm^3$.

XEROSTOMIA Xerostomia is a marked reduction in salivary gland secretion. Clinical symptoms and signs of xerostomia include dryness, a sore or burning sensation (especially involving the tongue), cracked lips, slits or fissures at the corners of the mouth, changes in the tongue surface, and increased frequency or volume of fluid intake. A preventive oral care regimen must be initiated to halt the destruction. Xerostomia can result from the inflammatory and degenerative effects of ionizing radiation on salivary gland parenchyma, especially serous acinar cells. These changes are often rapid and irreversible, especially when the salivary glands are included in the radiation fields. Salivary flow measurably decreases within 1 week after starting treatment and diminishes progressively with continued treatment. The degree of dysfunction is related to the radiation dose and volume of glandular tissue in the radiation field. Xerostomia alters the mouth's buffering capacity and mechanical cleansing ability, often contributing to dental caries and progressive periodontal disease.

RADIATION NECROSIS Necrosis and infection of previously irradiated tissue (osteoradionecrosis) is a serious complication for patients who have undergone radiation for head and neck tumors. Radiation-induced oral complications require aggressive dental therapy before,

during, and after radiation therapy to minimize the occurrence of severe sequelae: permanent xerostomia, ulcerative caries, radiation-induced osteomyelitis, and osteoradionecrosis.

Intervention Options

ORAL CARE CONSIDERATIONS Routine systematic oral hygiene is extremely important in reducing the incidence and severity of the effects of oncologic treatment such as radiation caries, mucositis, and stomatitis. In patients with mild, occasional xerostomia or with resection involving oral structures, an inspection identifies areas that require attention. Oral hygiene methods include rinsing or irrigation and mechanical plaque removal. Telling pet owners how to perform mouth care is just as important as informing them how to administer a medication. After meals, the oral cavity should be rinsed or wiped; wiping the oral cavity is almost always necessary for patients with xerostomia. Rinsing the oral cavity may not be sufficient for a thorough cleansing of the oral tissues. After a routine is developed, mechanical plaque removal may be necessary to assist rinsing. Mechanical plaque removal includes use of gauze, toothettes, toothbrush, and interdental aids such as floss, proxybrush, wooden wedge, or denture brush. Toothettes do not thoroughly cleanse the dentition, although they work very well to clean surgical areas following maxillectomy or hemimandibulectomy. Toothettes are also good for cleaning the maxillary and

mandibular alveolar ridges of edentulous areas, the palate, the palate with a prominent torus, and the tongue. If xerostomia is present, plaque is thicker and heavier than usual and will not rinse away. Oral care products should be selected carefully; those that produce symptoms or injure the mucosa should not be used. Rinses containing alcohol should be avoided. Since the flavoring agents in toothpastes can irritate or burn gingiva and mucosa, a mild toothpaste should be chosen, such as a child's toothpaste. Lip care is important and should include using a moisturizer.

MANAGEMENT OF MUCOSITIS AND STOMATITIS Oral care protocols generally include atraumatically cleansing the oral mucosa, moisturizing the lips and oral cavity, and relieving pain and inflammation. A soft toothbrush or foam swab (toothette) cleans teeth effectively and atraumatically. Options for cleansing and debriding agents include salt and soda (1/2 teaspoon each of salt and sodium bicarbonate in 8 ounces of warm water), normal saline, sodium bicarbonate (1 teaspoon in 8 ounces of water), sterile water, and hydrogen peroxide (diluted 1:1 with water or normal saline). Indications for use of hydrogen peroxide include crusting and need for gentle debridement. Use should be time limited (for 1 or 2 days maximum) since chronic use may impair timely healing of stomatitis. In patients with stomatitis, irrigation or rinsing with mild saline or salt and soda should

be performed every 2 hours. Gentle wiping with wet gauze immersed in a saline solution aids in removal of debris. Toothettes may be too harsh for some areas. Irrigation should be performed prior to topical medication, as removal of debris and saliva allows penetration to the oral tissues and prevents material from accumulating. Frequent rinsing cleans and lubricates tissues, prevents crusting, and soothes sore gingiva and mucosa. Frequent rinsing also removes debris and prevents debris and bacteria from accumulating. Agents that produce symptoms or injure the mucosa should not be used. Toothpaste may be used if tolerated; however, over-the-counter mouthwashes generally contain alcohol and should be eliminated. Glycerin is hygroscopic (i.e., takes up and retains moisture) and may dry tissues. Topical anesthetics may minimize pain temporarily but are frequently formulated with excipient ingredients (additives) that can intensify and prolong mucositis. Systemic analgesics (including opioids) are indicated to alleviate discomfort, but veterinarians need to be aware of agents that produce gastrointestinal irritation or affect hemostasis.

MANAGEMENT OF INFECTION Prophylaxis against fungal superinfections is generally recommended and includes use of topical antifungal agents such as nystatin-containing mouthwashes. Although topical antifungal prophylaxis and treatment may clear superficial oropharyngeal infections, topical agents are not well absorbed and are ineffective against more deeply invasive fungal

infections, which typically involve the esophagus and lower gastrointestinal tract. For this reason, systemic agents are indicated for treating all except superficial fungal infections in the oral cavity. Chlorhexidine oral rinse has been used in combination with fluoride gel to control cariogenic flora in humans. Veterinarians should note that chlorhexidine oral rinse may be used as a mouthwash during routine dental hygiene examinations under anesthesia to prevent ingestion. Commercially marketed formulations may also contain appreciable quantities of alcohol, which may exacerbate xerostomia. This may be particularly important in the context that xerostomia may change flora to more cariogenic types.

MANAGEMENT OF CANDIDIASIS Candidiasis is a yeast infection that is generally an overgrowth of the fungus *Candida albicans*. The management of candidiasis may include (1) cleaning the oral cavity prior to taking antifungal medication, irrigation and mechanical plaque removal may be necessary; (2) discarding toothbrush and replacing it with a new one after each use; and (3) disinfecting any object or appliance used in the mouth (e.g., mouthpiece used during radiation therapy).

MANAGEMENT OF HEMORRHAGE The use of toothbrushes and dental floss in patients with platelet counts of less than $50{,}000/mm^3$ is controversial because of the potential to induce bleeding with routine oral care. Topical thrombin can be used for local hemostasis in

patients with minor oral hemorrhage secondary to thrombocytopenia.

MANAGEMENT OF XEROSTOMIA It is imperative that patients who have xerostomia maintain oral hygiene to prevent dental problems. Periodontal disease can be accelerated and caries can become rampant, unless preventive measures are instituted. To prevent dental decay when xerostomia is involved, pet owners should (1) perform systematic oral hygiene at least 4 times per day (after meals and before retiring at night), (2) rinse the mouth with a solution of salt and baking soda 4–6 times per day ($^1/_2$ teaspoon salt and $^1/_2$ teaspoon baking soda in 8 ounces warm water) to clean and lubricate the oral tissues and to buffer the oral environment, (3) avoid foods and liquids with a high sugar content, and (4) have free access to water to alleviate mouth dryness.

Other Considerations

Client education and patient supportive care are important for pets experiencing oral complications related to cancer therapy. It is important to closely monitor patients' distress, ability to cope, and their response to treatment (quality of life); to show concern for the problems they are experiencing; and to educate and support the pet owner. With full support from the veterinary staff, the patient and the pet owner can be expected to be able to deal with these complications.

Malignant Effusions

Effusions may be the presenting sign of cancer or they may develop after the cancer is diagnosed. Only 50% of the effusions that develop in cancer-bearing pets during the course of their illness are malignant. Correct diagnosis of the cause of pleural effusions is the necessary first step in their management.

Pleural effusions are caused principally by congestive heart failure, malignancy, and infection. Pets commonly present with the symptoms of cough, dyspnea, decreased exercise tolerance, and chest pain. While larger effusions may be detected on physical examination, radiographs or ultrasound of the chest may detect effusions as small as 100 ml. A diagnostic thoracentesis should be performed early in the course of investigation. In markedly symptomatic pets, removal of pleural fluid can provide immediate, albeit temporary, relief; generally 250–500 ml or more must be removed to improve symptoms. Pleural fluid analysis should include protein, pH determination, cell counts, cytology, and cultures for bacteria, fungi, and mycobacteria. At least 50 ml of pleural fluid is necessary for adequate cytologic examination.

Pleural effusions are classified as transudative or exudative. Most often, transudative effusions are caused by congestive heart failure, cirrhosis, nephrotic syndrome, or occasionally by lymphatic blockade produced by cancer. Exudative effusions are caused by infection or malignancy. In the absence of infection, an exudative

pleural effusion, especially if it is bloody, strongly suggests a malignant etiology. The cancer very likely causes an exudative pleural effusion in a pet with a current or past cancer. Effusions due to lymphoma or mediastinal involvement by any tumor may be chylous and cytologically negative. About half of effusions ultimately diagnosed as malignant have a positive cytology from the initial thoracentesis.

Diagnostic Approach

Two different approaches can be used to attempt to diagnose the etiology of pleural effusions if the initial cytologic examination does not show malignant cells. Repeat thoracentesis and pleural biopsy will confirm malignancy in 80–90% of malignant effusions. The pleural biopsy has a higher complication rate but a higher yield than thoracentesis. Despite thoracentesis and pleural biopsy, 10–20% of pets with malignant pleural effusions still have no diagnosis. In such pets, thoracoscopy or thoracotomy is needed for diagnosis. Although thoracoscopic biopsy requires local or general anesthesia, it increases the diagnostic yield greatly compared to thoracentesis.

The alternative diagnostic approach to pets with pleural effusions whose initial cytologic examination does not show malignant cells is to go directly to thoracoscopy or thoracotomy with biopsy of visually identified abnormal areas of the pleura. The diagnostic yield of a

malignancy using this approach exceeds 90% if the effusion is caused by cancer.

Treatment Considerations

Once the diagnosis of malignant pleural effusion has been made, treatment depends on the tumor type and prior, if any, antineoplastic therapy. About 25% of effusions require no immediate therapy; the effusions are small and stable. Malignant effusions caused by lymphomas may respond to systemic chemotherapy. Repeated percutaneous draining of effusions may lead to tumor growth along the needle track and through the chest wall. Pets who have received extensive prior systemic therapy and those with chemotherapy-resistant tumors are not likely to respond to systemic therapy. Palliative approaches to the management of malignant pleural effusions are necessary in such pets.

Pets with symptomatic malignant pleural effusions whose underlying cancer is unlikely to respond to systemic treatment should have their pleural fluid drained. Pets with relatively large (>1,000 ml) recurrent effusions whose symptoms resolve with drainage and whose lungs can fully expand are candidates for palliation. Two general approaches to the palliative management of symptomatic pleural effusions are chest tube drainage with installation of a sclerosing agent and thoracoscopic drainage of the pleural effusion under local or general

anesthesia with intraoperative sclerosis of the pleural space.

Historically, many chemical agents have been instilled into the pleural space and shown to have some effectiveness in controlling effusions, including tetracycline, doxycycline, minocycline, bleomycin, cisplatin, doxorubicin, mitoxantrone, interferon, *Corynebacterium parvum*, methylprednisolone, and talc.

Chest tube drainage should be done by inserting the chest tube into the pleural cavity and draining the fluid. When the drainage reaches less than 50–100 ml in a 24-hour period, a sclerosing agent can be instilled. Information on the recommended sclerosing agent is currently inconclusive. Small numbers and relatively short follow-up plague the few randomized studies on this topic. Some comparative studies suggest advantages for talc as the sclerosing agent compared to tetracycline and others. In humans with breast cancer, thoracoscopy and insufflation of talc controlled the pleural effusions in twice as many patients as tetracycline (>90% versus 50%, respectively).

Another approach that is appropriate for pets with a symptomatic malignant pleural effusion and good performance status who are capable of undergoing a procedure under local, regional, or general anesthesia is a thoracoscopy with biopsy of suspicious pleural lesions, lysis of any adhesions, evaluation to see if the lung reexpands, and instillation of the sclerosing agent during the

same procedure. This could shorten the hospitalization because the whole procedure can be done in the operating room in a single day. Since tetracycline is no longer available and similar efficacy has been shown for doxycycline, doxycycline has been substituted for tetracycline in human clinical trials. Pleural stripping (pleurectomy) via thoracotomy or thoracoscopy is nearly 100% effective in controlling malignant pleural effusions, but the morbidity is so severe that this procedure is rarely used in veterinary medicine.

Prognosis

The prognosis for dogs and cats with malignant pleural effusions is poor—median survival time with treatment is about 6 months—and in those with chemotherapy-resistant tumors that are not likely to respond to systemic therapy, the prognosis is grim.

Oncology Emergencies

Cancer itself can present as an emergency. Internal blood loss from a ruptured abdominal mass or a pericardial effusion due to a bleeding heart-based tumor may present as shock. General and emergency veterinarians who are able to recognize these signs early and institute appropriate shock therapy can give these patients and their owners' time, a tissue diagnosis, and treatment options for extended high-quality time.

Other examples of oncologic emergencies include metabolic derangements (hypercalcemia, hypoglycemia, and hyponatremia).

The treatment of cancer can also lead to many unique yet predictable complications. The administration of many chemotherapeutic agents is associated with known side effects. Many of these agents irritate tissues, and extravasations will occur even to the most experienced oncologist. Some agents are associated with hypersensitivity reactions and even anaphylaxis. Many side effects are predictable. Bone marrow suppression and gastrointestinal disturbances are just some common complications of these agents.

Metabolic Complications

Hypercalcemia is the most common metabolic disturbance associated with neoplasia. Most commonly the result of parathyroid-related peptides produced by some tumors, hypercalcemia is usually caused by lymphoma. Other tumors frequently implicated include anal sac adenocarcinoma, mammary adenocarcinoma, and primary hyperparathyroidism. Emergency care for the hypercalcemic patient involves a diuresis with 0.9% NaCl for enhanced calciuresis. Furosemide (2–4 mg/kg bid) also enhances calcium elimination. Other drugs used to treat hypercalcemia include intravenous biphosphonates (etridronate, disodium palmidroate), gallium nitrate, mithramycin, and salmon calcitonin. Corticosteroids

prevent bone reabsorption, intestinal absorption, and increase urinary calcium excretion. However, because of their rapid antitumor effects, corticosteroid use should be withheld until a tissue diagnosis is made. Identification and treatment of the primary disease becomes the highest priority. Lymph node aspiration and biopsy, chest radiographs, abdominal ultrasound, and bone marrow evaluation should follow physical examination, including lymph node palpation and perianal examination. Every effort should be made to rule out lymphoma and anal sac adenocarcinoma.

Hypoglycemia associated with neoplasia may result from an insulin-secreting tumor, destruction of normal gluconeogenic tissues, or glucose consumption associated with such systemic complications as bacterial sepsis. The most common tumors associated with hypoglycemia are insulinoma, hepatoma, and carcinoma. Insulinomas are diagnosed by demonstrating inappropriately high levels of insulin in the face of hypoglycemia. Animals showing clinical signs of hypoglycemia (stupor, coma, seizures) can be treated with parenteral dextrose and dextrose-containing fluids. Prednisone (0.5–2 mg/kg divided bid) increases hepatic gluconeogenesis and antagonizes the effects of insulin on peripheral tissues. Diazoxide (10–40 mg/kg divided bid) can directly inhibit insulin secretion and may be useful in the medical management of insulin-secreting tumors. Surgical excision and medical management of metastatic lesions can lead to the temporary resolution of the clinical disease.

Shock

Animals with large intra-abdominal tumors may appear normal to the owner until such time that these vascular tumors rupture and lead to acute blood loss, collapse, and hypovolemic shock. Acute collapse can also be seen with pericardial tamponade secondary to vascular tumors on the heart or at the heart base. Both cases present with cool extremities, a rapid heart rate, decreased mentation, and hypotension. It is important to differentiate pericardial tamponade from hypovolemia, as aggressive fluid therapy may actually worsen the patient's condition. Jugular pulsation, elevated central venous pressure (distension of the lateral saphenous vein when held above the heart), decreased amplitude electrocardiogram, and a rounded cardiac silhouette are often seen with tamponade. Tamponade is best treated immediately with pericardiocentesis. Internal blood loss from a ruptured vascular tumor should be treated with shock doses of crystalloid fluids. Frequent rechecks of heart rate, blood pressure, and packed cell volume are mandatory. If the packed cell volume drops precipitously, whole blood, packed red blood cells, or cell-free hemoglobin should be used to improve blood oxygen content. Patients should be carefully evaluated to identify the source of the hemorrhage. When a patient's condition allows, radiographs of the chest and abdomen help stage the disease and provide the veterinarian and owner more information on the extent of the disease.

Exploratory surgery is necessary to remove the source of blood loss and fully evaluate the extent of the disease. The acute nature of these cases requires compassion and understanding from the veterinarian. The diagnosis of cancer when the only finding is an intra-abdominal mass can be overwhelming for owners. Clients need to be informed and given every option. Surgical exploration and biopsy are the only ways to definitively diagnose and treat these cancers.

Sepsis and septic shock are not uncommon in cancer patients. Sepsis can be the result of the disease itself or a complication of treatment. Intestinal neoplasia can lead to bacterial translocation and even rupture of a hollow viscus. These animals present with signs of acute abdominal distress and evidence of peritonitis on plain radiographs (free air, decreased abdominal detail). The diagnosis can be confirmed with a diagnostic peritoneal lavage. Animals with diffuse intestinal neoplasia may have a more chronic course of weight loss, panhypoproteinemia, and nonspecific gastrointestinal symptoms, which may lead to weakened immunity and septic complications. Septic shock is characterized by fever or hypothermia, leukocytosis or leukopenia, and hypotension associated with the systemic release of local inflammatory mediators. Emergency management of these cases centers around the quick identification and removal of the septic focus, appropriate antibiotic therapy, and cardiovascular support with fluids, colloids, and if necessary, positive inotropes.

Extravasation

Some of the more common chemotherapeutic agents used in veterinary medicine can cause significant tissue injury when they extravasate into perivascular tissues. Some of the more serious compounds include the vinca alkaloids (vincristine and vinblastine) and doxorubicin. Other agents causing tissue damage include mithramycin, mitoxantrone, and cisplatin. Every effort should be made to prevent extravasation. Veins used for chemotherapy should not be used for blood sampling. Multiple attempts to catheterize one vein or recent venipunctures make the vein unsuitable for administration of any cytotoxic drugs. A careful "first-stick" approach using a small (22–23 g) catheter should be used to administer large volumes of drugs like cisplatin and doxorubicin. Small volumes (<1 cc) can be given through a small (23–25 g) butterfly catheter. Saline should be flushed before and after administration of the chemotherapeutic to assess catheter placement and ensure vessel integrity. The earliest sign of extravasation is pain. Animals become extremely agitated, even to the point of self-trauma, as these vesicants leak into surrounding tissues. Erythema may develop quickly or over several days, ultimately resulting in tissue necrosis and open, draining wounds. When extravasation is suspected, do not remove the catheter. Instead, use the catheter to remove as much drug as possible. Apply *warm* compresses to enhance systemic absorption. Then

apply *cold* compresses to affected area for up to 10 hours to inhibit cytotoxicity. Keep in mind that, even with the use of good first aid, intense wound management may be required.

Anaphylaxis

Allergic complications are not common side effects of chemotherapy. Reactions range from potentially lethal anaphylaxis to mild, delayed hypersensitivity reactions. Serious anaphylaxis has been associated with L-asparaginase. Because L-asparaginase associated anaphylaxis usually occurs within minutes, it is advisable to observe the patients for no less than 30 minutes after administration. Giving the drug by intramuscular injection can minimize the risk of anaphylaxis. Intravenous and intraperitoneal administration is associated with higher incidence of anaphylactic reactions. Anaphylaxis causes acute collapse and hypotension. Emergency management of these patients involves quick shock therapy. Intravenous access and shock volumes of crystalloid fluids (up to 90 ml/kg/hr) are given along with 0.1–0.3 ml of a 1:1000 dilution of epinephrine given IV or IM. Delayed hypersensitivity can be seen with any drug but has been most commonly associated with doxorubicin, etoposide, and paclitaxel. These reactions typically result in erythema and swelling of the ears, face, and paw. Delayed hypersensitivity reactions can be minimized by diluting drugs such as doxorubicin with 250–500 ml of 0.9% NaCl and

administering them slowly over 30 minutes. Hypersensitivity reactions can be treated with rapid acting corticosteroids, dexamethasone sodium phosphate (2 mg/kg IV), and an antihistamine, diphenhydramine (2–4 mg/kg IM).

Acute Tumor Lysis Syndrome

Acute (hours to days) collapse and even death can be seen with the treatment of extremely chemosensitive tumors. The destruction of large tumor volumes can lead to massive release of inflammatory cellular debris. The resulting inflammatory cascade can mimic sepsis and septic shock and can best be described as a systemic inflammatory response. Electrolyte disturbances caused by the release of intracellular potassium and phosphorous also contribute to cardiovascular problems. The tumors most frequently associated with acute lysis include lymphoma and leukemia. Fast recognition of tumor lysis with appropriate cardiovascular support is required if the patient is to survive. Bradycardia in the face of shock should alert the clinician to possible hyperkalemia. Hypocalcemia may result from high phosphorous levels and can result in impaired cardiac conduction and reduced cardiac output. Aggressive fluid resuscitation, normalization of electrolytes, and support of cardiac output and vascular tone are necessary to see the patient through the crisis.

Neutropenia

Bone marrow suppression is an expected complication of many chemotherapeutic protocols. In addition, diseases like leukemia and lymphoma can invade the bone marrow, causing primary granulopoiesis and even pancytopenia. Drugs that are highly myelotoxic include doxorubicin, cyclophosphamide, cisplatin, and carboplatin. Doxorubicin and cyclophosphamide usually cause myelosuppression in 7–10 days. Recognizing the neutrophil nadir and taking steps to prevent bacterial colonization should help prevent serious complications. Patients should be closely monitored during this period. Changes in appetite, attitude, body temperature, mucous membrane color, and pulse quality warrant closer examination. Every effort should be made to prevent bacterial colonization during periods of neutropenia. Signs of bacterial colonization will also be affected by neutropenia. Bacterial colonization of lungs and bladder can result in infection without suppurative inflammation. Culture of urine, blood, and bronchial fluid can result in the identification of causative organisms without cellular evidence of inflammation. Treatment of neutropenia and septic complications is directed at maintaining perfusion through the use of crystalloid and colloid solutions and antibiotic therapy with bactericidal drugs effective against likely organisms. Recombinant human granulocyte colony-stimulating factor (5 μg/kg/day SQ) can be administered to neutropenic

patients to decrease the duration and severity of chemotherapy induced neutropenia.

Gastrointestinal Ulceration

Upper GI inflammation can be managed with antacids and GI protectants. Symptoms of inflammatory colitis can be managed with sulfasalazine, 10–30 mg/kg tid. Many chemotherapeutics stimulate the chemoreceptor trigger zone to cause a central nausea. Secondarily, the primary disease can cause stimulation to the gastrointestinal tract and peritoneal cavity, resulting in nausea and vomiting. Early antiemetic therapy should be considered in anorectic nauseous patients. Chemotherapy-induced emesis is mediated by 5-HT_3-serotonergic receptors. Antiemetic drugs, which antagonize this receptor, seem to work the best. Metoclopramide (1–2 mg/kg/day) has some partial 5-HT_3-antagonist properties and can be given by continuous infusion. Specific 5-HT_3 receptor antagonists such as ondansetron (0.5–1.0 mg/kg), although expensive, work even better.

Diarrhea

Simplified, diarrhea is the result of increased fecal water. A number of different pathophysiologic mechanisms can account for increased fecal water. Acute diarrhea is most often caused by malabsorption (osmotic diarrhea), abnormal fluid secretion (secretory or inflammatory diarrhea), and altered intestinal motility. Mucosal or

submucosal diseases that impair absorption in either the small or large bowel result in malabsorptive diarrhea. Impaired absorption of dietary substances interferes with water resorption by altering osmotic gradients. Mucosal diseases also may directly impair sodium resorption, in effect inhibiting water resorption, resulting in diarrhea. Enhanced intestinal secretion of water and electrolytes can be induced by several stimuli, most notably bacterial enterotoxins. Bile acids and dietary fatty acids also incite intestinal secretion, as does intestinal obstruction. Damage to the intestinal mucosa can result in transudation of water and electrolytes. If the injury is severe, plasma proteins and blood may also be lost. It is unclear whether a diarrhea can be caused specifically and only by abnormal motor function. Most diarrheal diseases that have been studied have been shown to alter intestinal fluid and electrolyte transport as well as smooth muscle function. Intestinal motility, most notably segmental contractions, is reduced in most diarrheic conditions. Decreased segmental contractions result in transport of ingesta at a rate too fast for digestive and absorptive processes to occur. Diarrhea may result from one pathophysiologic mechanism; however, in most patients with diarrhea, more than one pathophysiologic mechanism is simultaneously operative.

Mild diarrhea causes few metabolic consequences; however, moderate or severe diarrhea may lead to profound hydration and electrolyte and acid-base disturbances. Diarrhea most often results in loss of fluids

isotonic to plasma. Loss of isotonic fluid decreases circulating plasma volume and, if severe, precipitates hypovolemic shock. The major solutes lost with diarrhea are sodium, chloride, and potassium. Initially, serum electrolyte concentrations remain normal because isotonic fluids are lost. Hypokalemia is the most common electrolyte disturbance. Renal loss secondary to aldosterone released in response to fluid volume depletion is the most important source of potassium loss. Significant losses of potassium may also occur through the feces if the diarrhea is severe or protracted. Metabolic acidosis may develop secondary to the loss of intestinal bicarbonate and the production of lactic acid by anaerobic metabolism in response to hypovolemia.

As with any medical problem, treatment for acute diarrhea is best based on knowledge of the cause. In many cases, however, the cause of acute diarrhea is not ascertained because of the anticipated brevity of the diarrhea, financial constraints of the owners, or the elusive nature of the disease process. As a result, symptomatic therapy of diarrhea is often utilized. Symptomatic therapy is also of importance in the adjunctive supportive therapy in patients with acute diarrhea in which the primary cause is known. The routine use of nonspecific antidiarrheal drugs in all patients with acute diarrhea is unnecessary and in many situations these agents are contraindicated.

Opiates stimulate segmental contractions and decrease peristalsis. The net effect is prolonged intestinal

transit that allows additional time for fluid and electrolyte absorption. Opiate actions are attributed to the direct effect on intestinal smooth muscle. Additional antidiarrheal effects are attributable to stimulation of absorption, and inhibition of secretion, of fluid and electrolytes. The two most common opiates used are loperamide (0.1 mg/kg PO q8hr) and diphenoxylate hydrochloride (0.1 mg/kg PO q8hr). Although structurally similar, loperamide appears to be more potent, have a more rapid onset of action, and have a longer duration of effect. These properties may be attributable to loperamide's prostaglandin synthetase inhibiting, calmodulin antagonizing, and calcium channel blocking actions. Side effects of these two drugs most often are noted when inappropriate dosages are used and include depression, vomiting, and excessive salivation. Opiates should not be used to treat acute diarrhea in which a bacterial cause is suspected. Increasing intestinal transit time prolongs residence time of the bacteria, allowing further proliferation of the organism, mucosal invasion, and the absorption of toxins. If diarrhea is not controlled within 48–72 hours, opiates should be discontinued.

Bismuth subsalicylate (0.5–1 ml/kg PO q6–8hr) appears to be an effective agent for the treatment of enterotoxigenic diarrhea. The salicylate moiety is felt to decrease intestinal secretion by interfering with prostaglandin production and by a more direct but undetermined effect on the enterotoxin. In addition, this drug appears to be anti-inflammatory, possess some

bactericidal activity, and may bind enterotoxin. Salicylate intoxication can result from overdosage, particularly in cats. It is a useful and practical therapy for acute nonspecific diarrhea. Silicates, such as kaolin, may bind enterotoxins but have no proven efficacy for the treatment of diarrhea.

Anticholinergics inhibit Cl^- and water secretion by crypt epithelial cells and stimulate Na^+, Cl^-, and water absorption by villus epithelial cells by antagonizing muscarinic (M_1 and M_2) cholinergic receptors. Unfortunately, available muscarinic antagonists are nonselective and also inhibit smooth muscle contraction, causing a major reduction in resistance to flow in the intestinal tract. For this reason, the effectiveness of these drugs is questionable and their use can precipitate ileus by further reducing intestinal motility in an animal with diarrhea whose intestine is already hypomotile.

Other drugs that might be of benefit in the treatment of severe, unexplained acute diarrhea would include 5-HT_3 antagonists (ondansetron or granisetron 0.5–1.0 mg/kg PO q12hr), a_2-adrenergic antagonists (clonidine 5–10 mg/kg SQ, PO q8–12hr), calmodulin antagonists (chlorpromazine 0.2–0.4 mg/kg SQ, IM q8hr or prochlorperazine 0.25–0.5 mg/kg PO, SQ, IM q8hr), and calcium channel blockers (verapamil or diltiazem 0.5–1.0 mg/kg PO). Because of limited clinical experience with the use of these drugs and their potential side effects, these drugs should be used with caution.

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Case Illustrations

CASE 1: Canine Osteosarcoma

A 6-year-old, 114-pound, castrated male Doberman presented with a 1-month history of left forelimb lameness. A soft tissue swelling was palpated overlying the distal radius of the left forelimb. Following palpation, the dog was unable to bear weight on the limb. Cytological examination of a fine-needle aspiration biopsy obtained from the soft tissues surrounding the left distal radius showed cells suggestive of a mesenchymal neoplasm. Radiographs of the thorax and abdomen were normal in appearance. An aggressive, destructive lesion of the left distal radius was observed radiographically and found to be highly suggestive of a primary bone neoplasm (Figure C1-1).

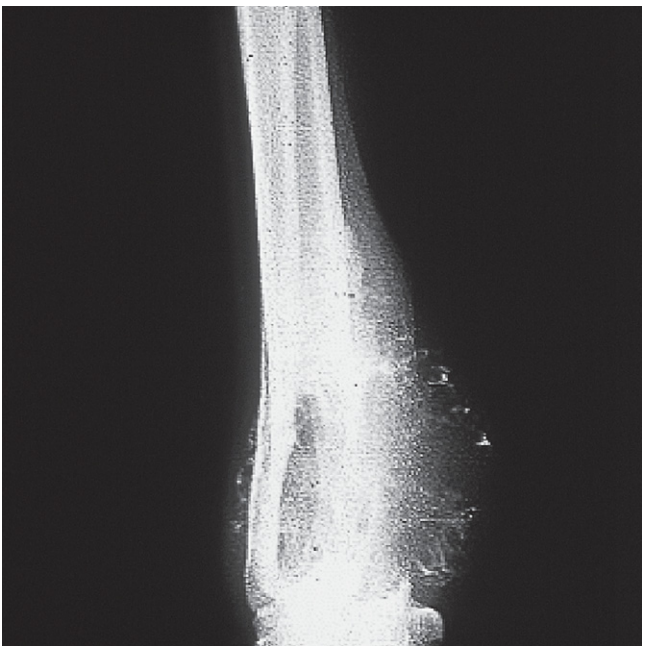

Figure C1-1 Survey radiograph of the distal radius.

A scintigraphic evaluation of the skeleton revealed no bony metastatic involvement but confirmed the aggressive nature of the primary neoplasm. The left forelimb was amputated and histological examination of the left distal radius confirmed a diagnosis of osteosarcoma (Figure C1-2).

The dog was given cisplatin chemotherapy once every 21 days for four treatments following the amputation. Seventeen months later, the dog presented with acute abdominal enlargement, weight loss, and depressed activity. Radiographic evaluation of the abdomen was suggestive of multiple hepatic metastatic nodules. The dog was euthanized, and metastatic disease was confirmed on postmortem examination.

Key Points

Most tumors of the musculoskeletal system have a brief clinical course prior to diagnosis (acute lameness). The most common bone tumor in the dog is osteosarcoma. These tumors progress rapidly with widespread microscopic metastatic lesions (micrometastases) present in virtually all tissues of the body. Because of the advanced stage at presentation (lysis of bone, possibly fracture), amputation of the affected limb is performed. To delay the growth of micrometastatic lesions, chemotherapy consisting of cisplatin, carboplatin or Adriamycin is given after amputation. Limb-sparing procedures have been reported but are rarely performed because of high cost and complications.

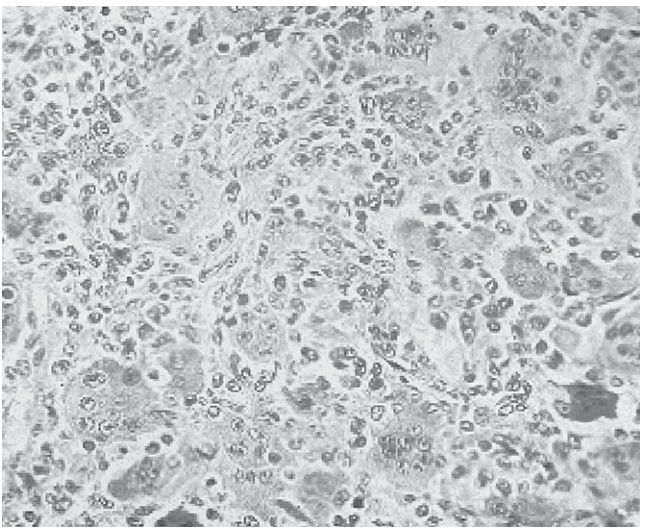

Figure C1-2 In this hematoxylin and eosin stain photomicrograph of osteosarcoma, note the disorganized architecture of the specimen and the presence of large, bizarre, multinucleated cells (osteoclasts).

CASE 2: Feline Cutaneous Melanoma

A 10-year-old, intact female, 8-pound domestic shorthair cat was presented with a 3-month history of multiple dermal melanomas on both ears. Several masses 3–8 mm in diameter were observed on each pinna (Figure C2-1). The masses were dark black in color, firm, fixed to the skin, but not painful on palpation.

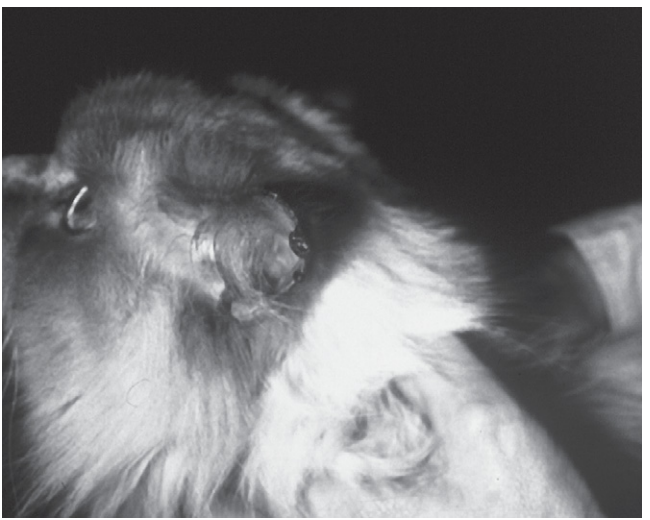

Figure C2-1 Multiple dermal melanomas on the left pinna.

Cytologic examination of cells obtained by fine-needle aspiration biopsy (Figure C2-2) showed plump spindloid to round cells containing melanin granules. Although the nuclei were obscured in most cells, a diagnosis of a well-differentiated melanoma was made.

The pinna was amputated. Histological examination of the surgical specimens confirmed a diagnosis of cutaneous melanoma. The cat has had multiple lesions confirmed as dermal melanomas arising along the face, neck, and body wall since the time of pinna amputation. All lesions have been excised and no evidence of lymph

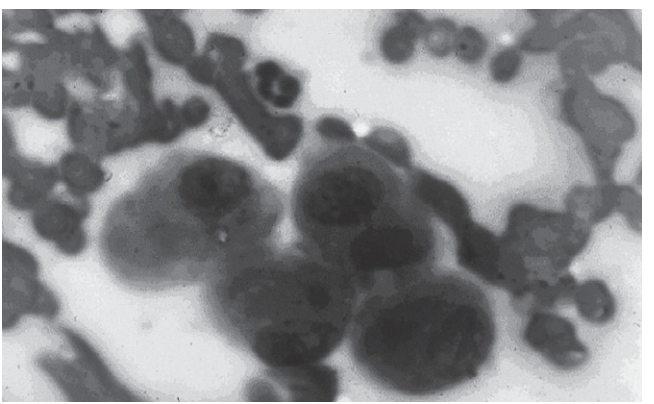

Figure C2-2 Dermal melanocytes observed on a cytologic smear obtained by fine-needle aspiration biopsy.

node or internal metastasis has been observed in the 12 months since the cat first presented to our hospital.

Key Points

Cutaneous melanomas are extremely rare in cats. Sites of occurrence that have been reported include the digits, head, and lumbar skin. Surgical removal is the treatment of choice, and metastases have been reported in one of five cats with dermal melanoma. Three of the remaining four cats were alive and disease free more than 1 year after surgery.

CASE 3: Canine Mast Cell Tumor

A 9-year-old, spayed female, 47-pound cocker spaniel mix presented with a 2-week history of a mass overlying the left midthoracic body wall. On examination, an 8-cm, soft tissue mass was palpated in the area of the 8th–11th mid-intercostal region. The mass was located in the subcutaneous tissues. Deep palpation revealed the mass to be deeply attached to the intercostal musculature. Findings of a complete blood count (CBC), serum biochemistry, and urinalysis were unremarkable. A fine-needle aspiration biopsy was performed, and examination was highly suggestive of a mast cell tumor (Figure C3-1).

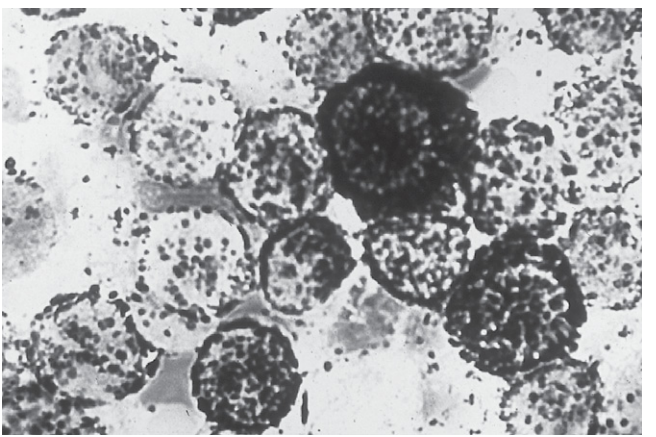

Figure C3-1 Cytological appearance of a mast cell tumor.

Radiographs revealed a soft tissue mass on the left thoracic body wall with no apparent invasion into the thoracic cavity. Ultrasonographic examination confirmed the deep attachment to the 8th through 11th ribs. No evidence of metastasis was noted within the liver, spleen, sublumbar lymph nodes, or thorax. The mass was excised with wide margins and "peeled" from the thoracic body wall. Histologic examination revealed neoplastic cells at the deep margin. A diagnosis of grade III mast cell tumor was made. The dog was treated with temporary radioactive iridium implants (Figures C3-2, C3-3, and C3-4).

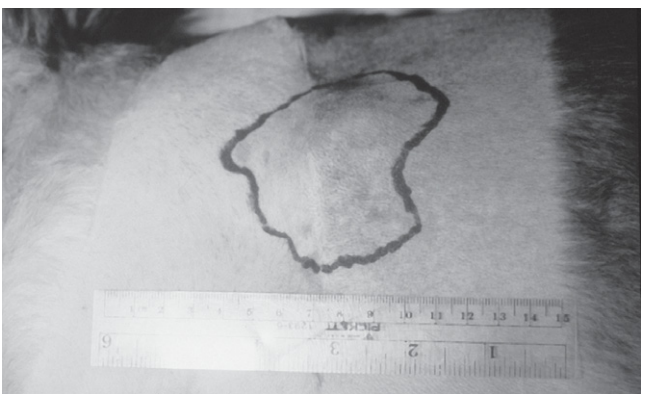

Figure C3-2 The grossly evident boundaries of the tumor are highlighted. The radiation field will extend 3 cm in all directions beyond these boundaries.

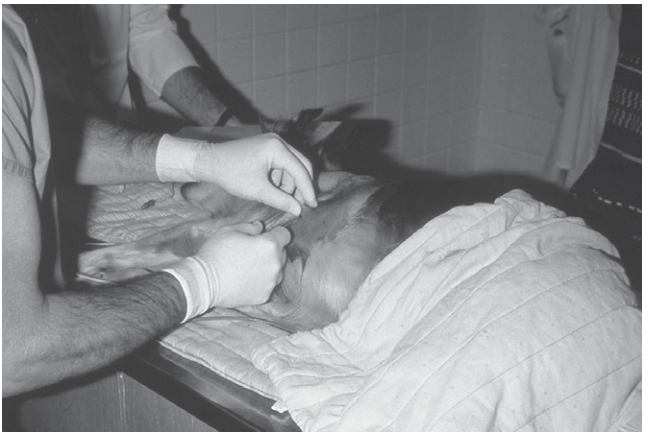

Figure C3-3 The dog is positioned in lateral recumbency under general anesthesia. Stylets are passed through the subcutaneous tissues, and several hollow tubes are placed at 1-cm parallel intervals (also see Figure C3-4).

The temporary implants were left in place until a uniform dose of radiation sufficient to "kill" the remaining cancer cells was obtained. The dose and time depend on the activity of the radiation packets. The advantage of an implant is that the distance the radiation travels is short, thus sparing the deeper normal tissues such as the

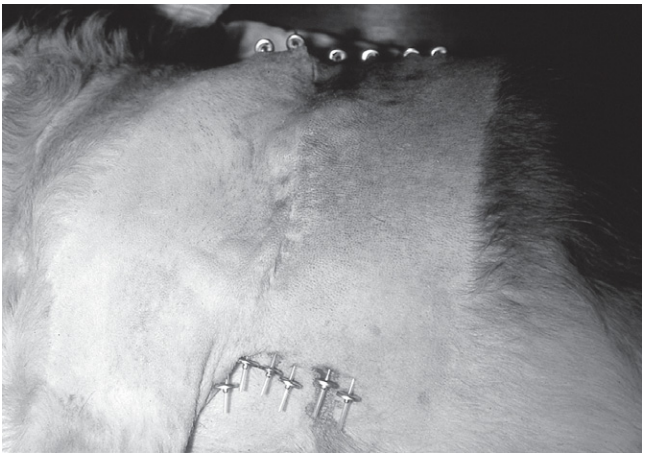

Figure C3-4 All tubes are placed, and the dog is transferred to the radiation isolation room. During recovery, each tube is loaded with a radioactive ribbon containing packets of iridium.

pleural space and lung. The radiation site became hyperemic and alopecic over the next 21 days; however, no signs of pleural or pulmonary toxicity occurred adjacent to the radiation site and no evidence of tumor recurrence or metastasis has been noted on repeated examination over the past 3 years.

CASE 4: Canine Thymoma

An 8-year-old, spayed female, 51-pound English springer spaniel was presented because the owner noticed a change in the sound of the bark. Radiographic, ultrasonographic, and magnetic resonance imaging (MRI) examination showed an extensive mediastinal mass that engulfed the cardiac silhouette on the right side and partially on the left. The mass was touching the mediastinal vessels but not invading them. The lung was totally obliterated on the right side. The left side of the lung was present but somewhat compressed. Cytologic examination was suggestive of round cell neoplasia, possibly thymoma. The anterior mediastinum was irradiated (Figure C4-1). Objective shrinkage of the tumor was noted during the therapy; however, 1 month following the end of therapy, the mass had enlarged to the preradiation size.

The dog was treated with weekly vincristine therapy for 2 months. The mass decreased in size by >90% during this time. Vincristine treatments were continued for an additional 6 months at 2-week intervals. Eight months after beginning vincristine treatment, the mass was not observed on survey radiographs of the thorax. The dog was still alive and in remission 19 months following treatment.

Key Points

Thymomas are malignant epithelial tumors containing mature lymphocytes and mast cells. Cytologic examina-

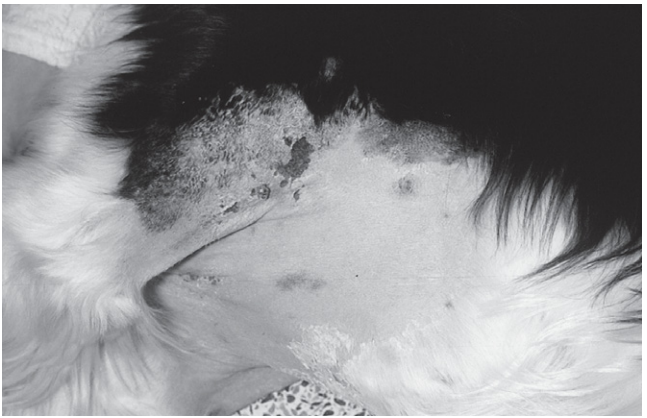

Figure C4-1 Note the alopecia and erythema that occurs late in the course of an external beam radiotherapy treatment of the thorax.

tion of cells obtained by fine-needle aspiration biopsy can be difficult. Differential diagnoses for an anterior mediastinal round cell tumor include lymphoma, thymoma, mast cell tumor (metastatic), or an undifferentiated endocrine neoplasm.

Common clinical signs in dogs with thymoma include cough and, less commonly, dyspnea and lethargy; some patients may have signs related to aspiration pneumonia secondary to myasthenia gravis and megaesophagus.

Thymomas tend to be large, invasive, slow-growing tumors with a low metastatic rate. Surgical excision with neoplastic-free margins is the treatment of choice. Dogs with megaesophagus, polymyositis, hypercalcemia, and aspiration pneumonia have a poor prognosis.

Success using either localized irradiation or systemic chemotherapy has not been described in a large number of dogs. Vincristine is commonly used in combination with other chemotherapy drugs in the induction, maintenance, and reinduction of remission in dogs with lymphoma.

CASE 5: Canine Bladder Tumor

A 14-year-old, spayed female, 34.5-pound mixed breed dog was referred for signs of stranguria, hematuria, and inappetence of 2 weeks duration. CBC findings were normal, the serum biochemistry showed increased blood urea nitrogen (BUN; 33). Survey radiographs of the abdomen showed a mass present in the trigone of the urinary bladder when contrasted with air (pneumocystogram; Figure C5-1).

An ultrasonographic examination of the abdomen showed a polyploid mass arising from the trigone region of the urinary bladder (Figure C5-2). Low-power resolution cytologic examination of a urine sample (free catch)

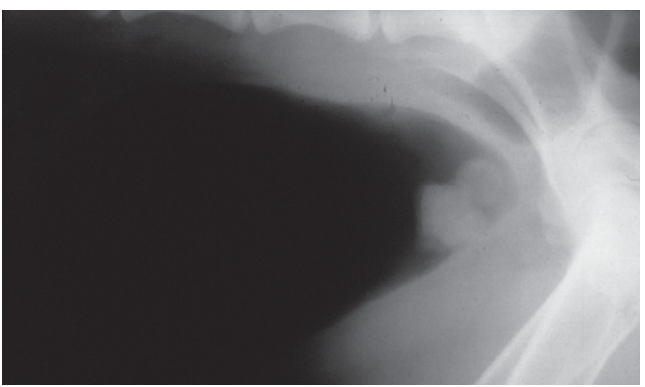

Figure C5-1 Pneumocystogram of the urinary bladder.

showed many neoplastic transitional epithelial cells (Figure C5-3).

Histologic examination of a biopsy obtained via a rigid cystoscope inserted into the distal urethra confirmed a diagnosis of transitional cell carcinoma (Figure C5-4). During the initial evaluation, the dog became unable to urinate and acutely azotemic resulting in depressed activity and inappetence. A temporary cystostomy procedure was performed, allowing diversion of urine through a Foley catheter (Figure C5-5).

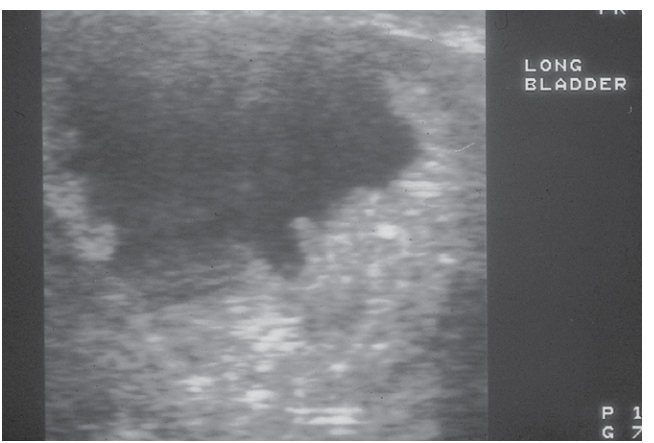

Figure C5-2 Ultrasonographic image of a urinary bladder mass arising from the trigone (lower right portion of the ultrasound image).

The dog was given two treatments of cisplatin chemotherapy. The temporary cystostomy tube was removed 2 months following the initiation of cisplatin therapy. The dog then was maintained on daily piroxicam chemotherapy. The dog was followed for 36 months; clinical signs of stranguria were reported rarely.

The dog had a persistently elevated BUN and creatinine with isothenuric urine, suggestive of chronic renal insufficiency as a result from either intermittent urinary outflow obstruction from the tumor or from the combination of cisplatin and piroxicam administration.

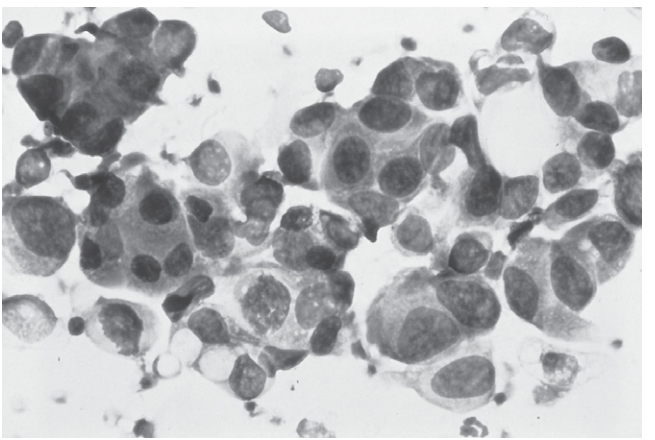

Figure C5-3 Low-magnification view of transitional epithelial cells from a urine sample.

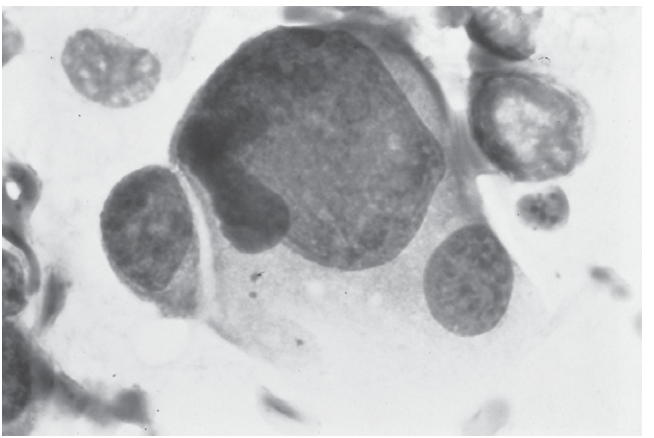

Figure C5-4 High-magnification view of a urine sample from a dog with transitional cell carcinoma.

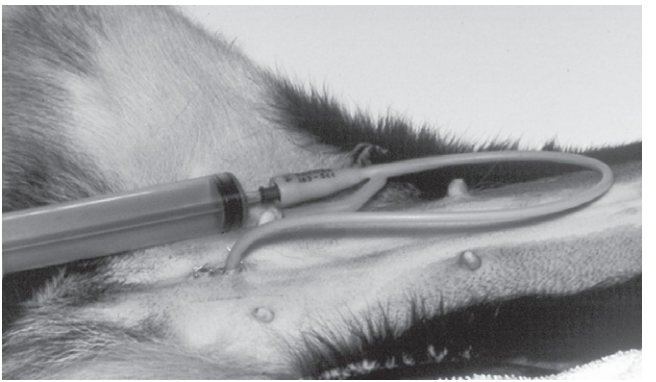

Figure C5-5 Foley catheter placement in a dog for urinary diversion during treatment of a transitional cell carcinoma.

CASE 6: Canine Lymphoma

A 5.5-year-old, intact female, 56.5-pound Doberman presented with a mass on the soft palate and weight loss (about 20 pounds) over the previous 6 months. The submandibular lymph nodes were enlarged (Figure C6-1) and the dog was having difficulty breathing.

A temporary tracheostomy tube (see Figure C6-1) was placed to relieve upper airway obstruction caused by enlarged lymph nodes. A CBC showed decreased packed cell volume (PCV; 30), hemoglobin (9.5 g/dl) and red blood count (RBC; 4.2 million/μl). No other abnormalities were noted. Cytological examination of a tissue

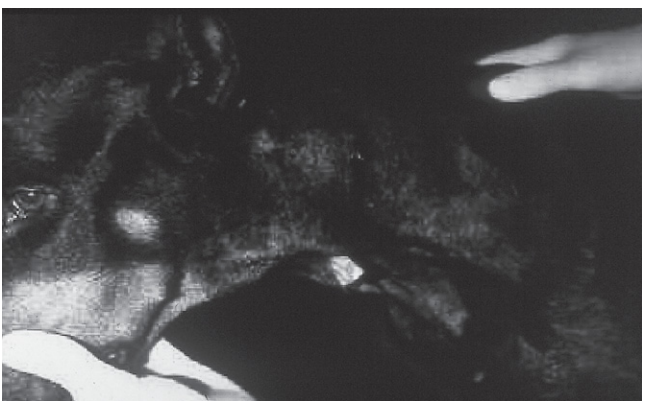

Figure C6-1 Enlarged submandibular lymph nodes in a Doberman.

imprint obtained from the mass in the caudal oropharynx progressing ventrally from the soft palate was suggestive of lymphoma. Survey radiographs of the nasopharyngeal region showed enlarged retropharyngeal lymph nodes (Figure C6-2).

The retropharyngeal lymph nodes were biopsied, and histological examination confirmed a diagnosis of lymphoma. The dog was treated with a combination of chemotherapy drugs including vincristine and Cytoxan. The retropharyngeal lymph nodes were irradiated in an attempt to palliate the signs of dyspnea. The dog died

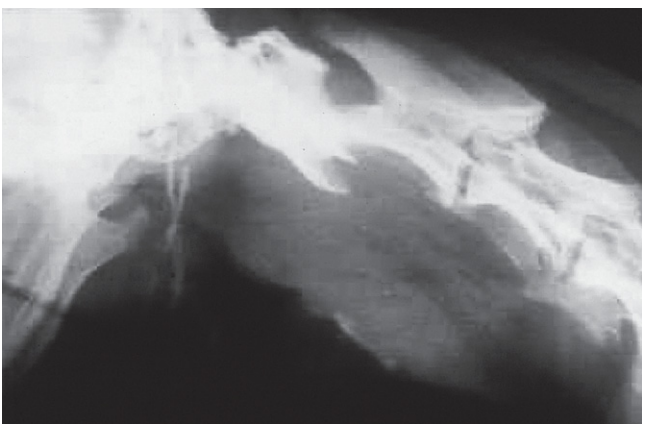

Figure C6-2 Survey radiographs showing enlarged retropharyngeal lymph nodes and tracheal compression. Thoracic radiographs were normal.

2 months following discharge from the hospital secondary to respiratory complications.

Key Points

Canine lymphoma is a multisystemic disorder of lymphocytic origin. Disease may originate in any one or all lymph nodes. Neoplastic cells, although few in number, can be readily identified in any organ of the lymphoreticular system (liver, spleen, bone marrow).

These tumors progress rapidly with widespread involvement, eventually affecting all lymph nodes with significant lymphocytic infiltrates present in the liver, lung, kidney, and bone marrow. Because of the advanced stage at presentation (lymph node enlargement, bone marrow involvement) and possible paraneoplastic syndromes (hypercalcemia, cancer cachexia), the lifespan of dogs is short without treatment (30–60 days).

The dog with lymphoma can be successfully treated, not cured, with chemotherapy. Many protocols exist that allow dogs to enjoy a significant, high-quality lifespan.

CASE 7: Canine Splenic Hemangiosarcoma

A 12-year-old, spayed female, 46-pound mixed breed dog was presented with a decreased appetite and lethargy. Enlarged popliteal lymph nodes and an abdominal mass caudal and ventral to the liver were palpated. A CBC showed a decreased PCV, hemoglobin, and RBC. Nucleated RBCs were noted as well as a decrease in platelet numbers. Serum biochemistry revealed an increased alkaline phosphatase and decreased potassium. Abdominal ultrasonography revealed masses within the spleen of mixed echogenicity. Thoracic radiographs showed possible neoplastic pulmonary infiltrates. A splenectomy was performed and a histologic diagnosis of hemangiosarcoma was made. The dog was treated with four cycles of Adriamycin. The dog died 15 months after surgery from complications due to metastases to the liver and lungs.

CASE 8: Canine Pituitary Macroadenoma

An 11-year-old, spayed female, 20.5-pound Boston terrier was presented for a decreased appetite and thirst, with estimated weekly episodes of confusion with weakness lasting about 24 hours. The dog had a history of skin tumors. A slight discharge from both nares was noted as well as mild bilateral cataracts. Several small masses on the cranium were noted and thought to be possible benign sebaceous adenomas. A firm 3-cm nonpedunculated mass was palpated on the left shoulder. Possible hepatomegaly was noted upon abdominal palpation. CBC findings were within normal limits. The serum biochemistry showed increased alanine transaminase (ALT; 398) and alkaline phosphatase (ALP; 458). An MRI showed a large enhancing mass arising from the region of the sella turcica. The primary consideration was a pituitary mass. A macroadenoma was diagnosed based on the MRI. The dog was treated with external beam radiation (25 daily 2-Gy fractions). The mass resolved and the dog was still doing well 2 years following radiation therapy.

CASE 9: Feline Vaccine-Associated Sarcoma

A 10-year-old, castrated male, 8.5-pound domestic shorthair cat presented with a 5-cm diameter, firm mass overlying the left scapula. The mass was first noticed 3 months ago and began to rapidly increase in size during the last 7 days. The mass was broad-based and fixed to the scapula. Thoracic radiographs were obtained and no pulmonary abnormalities were noted; however, two soft tissue masses were seen caudal to the last rib on the left lateral wall. No bony involvement was evident.

Ultrasonographic examination showed the mass infiltrating the tissues of the left paracostal region. Cytologic examination of a fine-needle aspiration biopsy revealed large, multinucleated, pleomorphic mesenchymal cells (Figure C9-1). The masses were excised (Figure C9-2) and submitted for histologic examination. A malignant spindle cell tumor, giant cell sarcoma (containing some areas that were morphologically consistent with osteosarcoma) was diagnosed.

The left scapular and thoracic wall region was irradiated using temporary subcutaneous iridium afterloading implants. Three months later, the cat presented with clinical signs of weakness and nonproductive coughing. Thoracic radiographs (Figure C9-3) showed an anterior thoracic mass and pleural effusion. Cytologic examination of a thoracocentesis sample confirmed metastatic disease and the cat was euthanized.

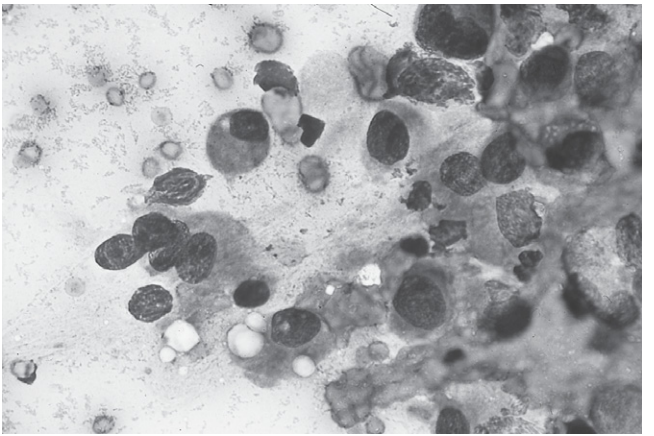

Figure C9-1 Wright-Giemsa stained fine-needle aspiration smear from the left scapular mass consistent with a mesenchymal neoplasm. Osteoid and malignant chondrocytes were observed in other areas, suggesting a diagnosis of either an osteosarcoma or giant cell tumor.

Key Points

Many investigations have suggested a causal relationship between vaccination and the development of tumors in cats. A Task Force by the American Veterinary Medical Association has been created to examine the cause(s) and treatment(s) of vaccine-associated

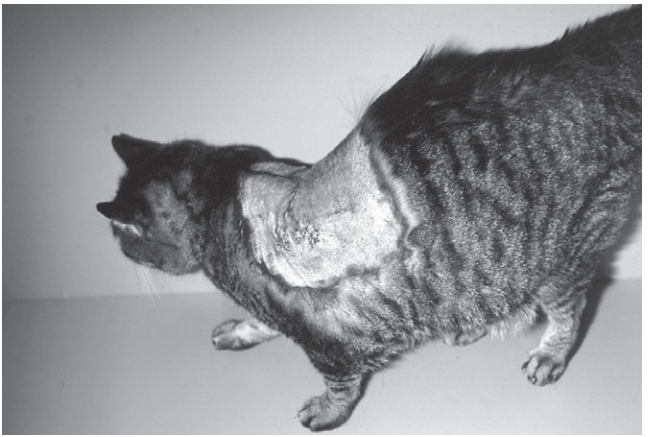

Figure C9-2 The shaved area illustrates the outermost extent of the surgical area. Neoplastic cells were observed at all surgical margins.

tumors in cats. Unfortunately, these tumors are quite invasive and surgical excision with neoplastic-free margins is uncommon. Regrowth following excision is sudden in onset, and preliminary reports regarding the use of radiation or chemotherapy have mixed results. Various histologic forms have been identified. Giant cell tumors are very uncommon in animals and known to be highly metastatic.

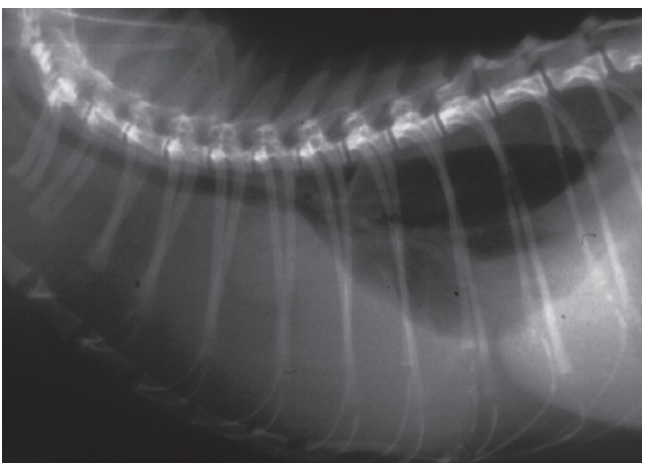

Figure C9-3 Thoracic radiograph showing an anterior thoracic mass with pleural effusion 3 months following irradiation for a vaccine-associated giant cell tumor.

CASE 10: Feline Bladder Tumor

An 11-year-old, castrated male, 8-pound domestic shorthair cat presented with hematuria. The cat had been urinating throughout the house and had no previous history of a urinary tract infection. On palpation, the bladder was found to be irregular and hard; however, no pain was noted.

The following laboratory findings were abnormal: decreased lymphocyte count, slightly increased eosinophil and basophil count, slightly elevated total protein, increased BUN (45), and increased total bilirubin (0.6). Urinalysis findings were specific gravity 1.033 with 3+ blood, 2+ bilirubin, 1+ ketones, 4+ protein, 8–10 white blood count (WBC)/high-power field (HPF), and loaded with RBC/HPF. Abdominal radiographs showed a large sublumbar lymph node, while the thoracic radiographs appeared normal. An ultrasound of the abdomen showed a large, irregularly marginated granular mass involving the wall of the urinary bladder that occluded the major portion of the lumen. Further evaluation showed a large medial iliac lymph node, and both kidneys showed diffuse increased echogenicity. Cytological examination of aspirates from the iliac lymph nodes and the bladder were diagnostic of squamous cell carcinoma.

Abdominal exploratory surgery was performed, the bladder isolated, and a 5-cm mass firmly attached to the mucosa of the bladder was removed (Figure C10-1). The iliac lymph nodes were biopsied. The surgical

margins contained neoplastic cells. The lymph nodes did not contain neoplastic cells. A diagnosis of squamous cell carcinoma was confirmed. The pet owner declined further therapy, and although the cat was free of clinical signs for 3 months, urinary tract obstruction occurred and the cat was euthanized.

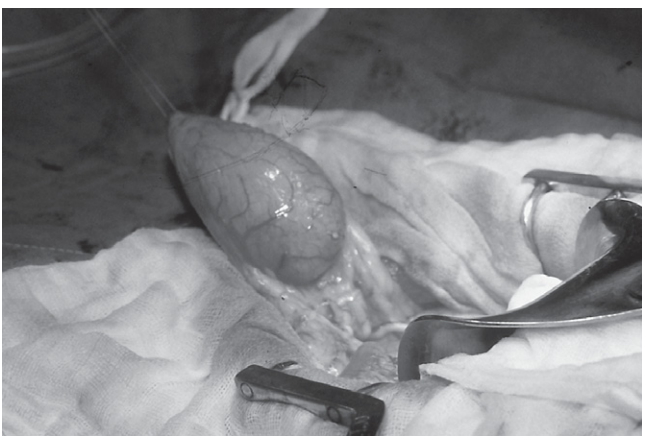

Figure C10-1 Exposed urinary bladder during a laparotomy. The bladder was opened and several biopsies obtained. Complete excision of grossly evident neoplastic tissue could not be performed.

Key Points

Tumors of the urinary bladder have a long clinical course prior to diagnosis. These tumors progress very slowly and signs can be misinterpreted for a complicated urinary tract infection. Because of the advanced stage at presentation, complete excision is often impossible. When tumors become evident on gross examination, only a small percentage of the tumor cells are responsible for further tumor enlargement (Gompertzian kinetics); therefore, many large-sized tumors are unresponsive to systemically delivered anticancer drugs.

CASE 11: Canine Mediastinal Lymphoma

A 5-year-old, intact male, 17-pound West Highland white terrier presented with a 2-week history of nonproductive cough, regurgitation, and enlarged lymph nodes. A generalized lymphadenopathy was noted on physical examination. The findings of a complete blood count were unremarkable. Results from a serum biochemical profile showed a slight elevation in glucose, alkaline phosphatase, and total bilirubin. Survey radiographs of the thorax showed enlargement of the anterior mediastinum mass. Equivocal hilar lymphadenopathy was also noted. A fine-needle aspiration biopsy of the left prescapular lymph node was diagnostic for lymphoma (Figure C11-1).

The dog was treated with a combination of Cytoxan, vincristine, and L-asparaginase. The dog was in complete remission for 7 months. The cancer then relapsed and was reinduced into remission for an additional 8 months using Adriamycin chemotherapy.

Key Points

Canine lymphoma is a multisystemic disorder of lymphocytic origin. The disease may originate in any one or all lymph nodes. Neoplastic cells, although few in number can be readily identified in any organ of the lymphoreticular system (liver, spleen, bone marrow). These tumors progress rapidly with widespread involvement, eventually

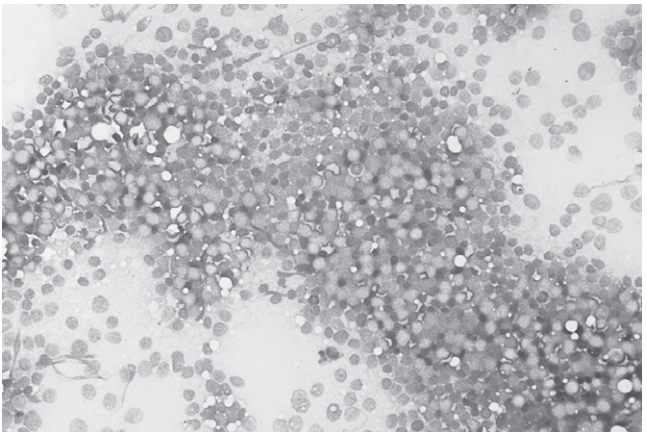

Figure C11-1 In this fine-needle aspiration biopsy specimen obtained from a superficial lymph node, note the pleomorphic features at low magnification.

affecting all lymph nodes with significant lymphocytic infiltrates present in the liver, lung, kidney, and bone marrow. Because of the advanced stage at presentation (lymph node enlargement, bone marrow involvement) and possible paraneoplastic syndromes (hypercalcemia, cancer cachexia), the lifespan of dogs is short without treatment (30–60 days). The dog with lymphoma can be successfully treated, not cured, with chemotherapy. Many protocols exist that allow dogs to enjoy a significant, high-quality lifespan.

CASE 12: Feline Intestinal Lymphoma

An 8-year-old, spayed female, 7.5-pound domestic shorthair cat presented with a 1-month history of lethargy, recent anorexia, and weight loss (3 pounds in the past 6 months). The cat had been recently tested and was FeLV/FIV negative. A bone marrow aspirate at the referring veterinarian showed significant lymphoproliferation. The cat was lethargic and recumbent, which had become normal to the owner in the past several months. An intestinal mass in the mid-abdomen was palpated. The CBC revealed a nonregenerative anemia, neutropenia, and thrombocytopenia. Results from a serum biochemistry profile were unremarkable. An ultrasonographic examination of the abdomen was performed. A mass in the abdomen appeared to be arising from the small intestine. A Tru-cut biopsy was obtained from the enlarged mesenteric lymph nodes. Histologic and cytologic examination of mesenteric lymph node specimens confirmed a diagnosis of lymphoma. The intestinal mass was removed (Figure C12-1) to relieve the obstruction. The cat was treated with single-agent asparaginase until neutrophil counts returned to normal. Then the cat was switched to a combination of vincristine and Cytoxan chemotherapy. The cat has been in remission for a period of 10 months.

In some cases, resection of the mass not only resolves the clinical signs of obstruction and the resulting anorexia and weight loss but also alleviates the need for

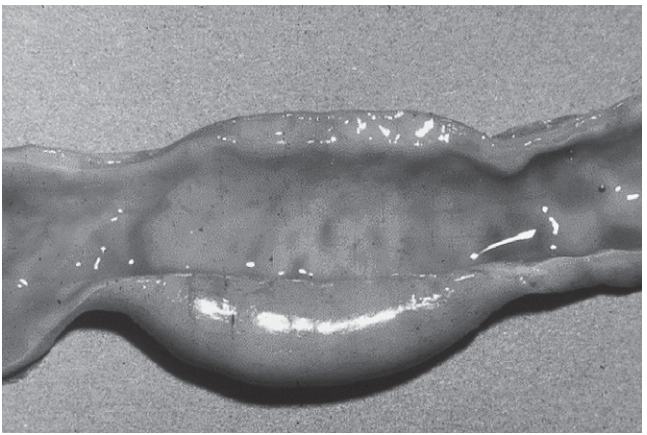

Figure C12-1 Intestinal lymphoma in a cat.

adjuvant chemotherapy. However, for the most part, lymphoma is a systemic disease and chemotherapy is needed to manage the disease.

Key Points

Feline lymphoma is a multisystemic disorder of lymphocytic origin. Feline leukemia virus infection has been shown to cause lymphoma in cats and a negative result of a test for the virus does not guarantee against prior exposure to the virus. As a retrovirus, FeLV can insert an "oncogene" into lymphocytes, resulting in uncontrolled

growth of the cells (i.e., cancer). The disease may originate in any one or all lymph nodes. Neoplastic cells, although few in number, can be readily identified in any organ of the lymphoreticular system (liver, spleen, bone marrow). These tumors progress rapidly with widespread involvement, eventually affecting all lymph nodes, with significant lymphocytic infiltrates present in the liver, lung, kidney, and bone marrow. Because of the advanced stage at presentation (lymph node enlargement, bone marrow involvement) and possible paraneoplastic syndromes (hypercalcemia, cancer cachexia), the lifespan of cats with no treatment is short (30–60 days).

The cat with lymphoma can be successfully treated, not cured, with chemotherapy. Many protocols exist that allow cats to enjoy a significant, high-quality lifespan. A positive test for FeLV indicates a poor prognosis. Because FeLV infects cells of the myeloid series, profound and sustained neutropenia can result following chemotherapy administration. In this cat, significant bone marrow infiltration with neoplastic cells resulted in neutropenia. To avoid further insult to the cells of the bone marrow, asparaginase was used.

CASE 13: Feline Mammary Carcinoma

A 13-year-old, spayed female, domestic shorthair cat was referred for treatment after a mammary tumor was removed 3 weeks ago. The biopsy from the referring veterinarian was diagnostic of adenocarcinoma/carcinosarcoma with evidence of lymphatic invasion. A large mass was palpated on the midline of the abdomen, along the previous incision site. A diagnosis following excision biopsy of mammary adenocarcinoma with lymphatic invasion was made.

The cat was treated with Adriamycin three times. Two months after beginning treatment, radiographs were suggestive of metastatic disease in the left caudal lung lobe. The cat was euthanized 3 months after beginning treatment, due to metastases.

CASE 14: Feline Lung Tumor

A 4-year-old, spayed female, 7.5-pound domestic shorthair cat presented with a 10-month history of a nonproductive cough and episodes of wheezing. On examination, the cat was found to have increased lung sounds and a nonproductive cough was elicited on tracheal palpation. The following laboratory findings were abnormal: slightly elevated PCV, total plasma protein (TPP), and an increased ALT. Thoracic radiographs revealed a solitary lung mass in the left caudal lung lobe and enlarged tracheobronchial lymph nodes (Figure C14-1). A surgical biopsy of the lung was cytologically examined, and squamous cell carcinoma with metastasis to the tracheobronchial lymph nodes was diagnosed.

Tumors of the respiratory tract are uncommon in cats. The most common clinical signs in cats with lung tumors are weakness, lethargy, and weight loss, not coughing or wheezing. Lung tumors tend to be solitary masses affecting the caudal lung lobes (left more than right) more than the cranial lung lobes, although pleural effusion may be noted in over 50% of cats, masking a mass or masses. If associated tracheobronchial lymph nodes are not enlarged, the median survival of cats is about 1 year following excision of a solitary lung tumor mass. The survival is poor (<60 days) in cats with poorly differentiated lung tumors or enlarged tracheobronchial lymph nodes.

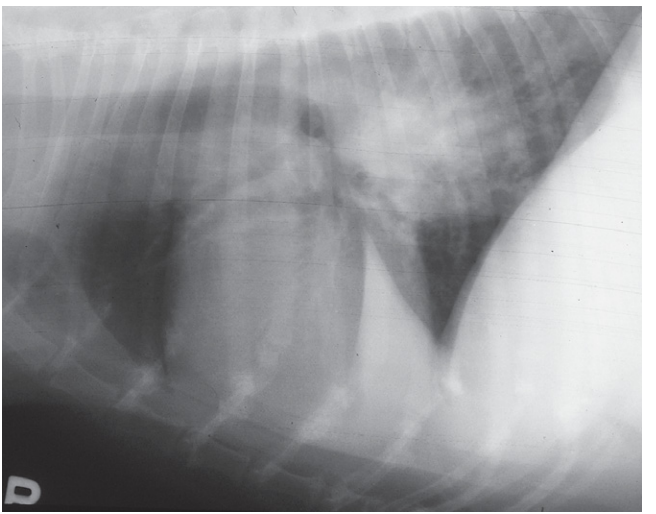

Figure C14-1 Right lateral thoracic radiograph of a cat. Note the solitary lung mass in the left caudal lung lobe and the dorsal deviation of the trachea by enlarged tracheobronchial lymph nodes. Because of the poor prognosis, the owner declined further therapy for the cat.

CASE 15: Canine Oral Melanoma

A 12-year-old, intact male, 63-pound golden retriever presented with a history of having growths removed from the oral cavity in the past. A round, pink mass on the right side of the soft palate was noted. The left submandibular lymph node seemed enlarged, and two small growths were noted (one on the right thoracic wall and the other on the middle dorsum, between the scapulae. The right prescapular lymph node was enlarged. A subdermal mass was noted over the right eye. Two or three hardened lumps were palpated in the testicle. Urinalysis showed specific gravity 1.024, pH 7, 4+ protein, 1+ bilirubin, negative for blood and hemaglobin, and 0–1 WBC + RBC/HPF. No other abnormalities were noted. Radiographs showed no evidence of thoracic involvement. Ultrasound showed testicular masses, most likely to be neoplasia. It also showed a focal enlargement of small bowel. Cytologic examination of an aspiration of the testicle was suggestive of an interstitial cell tumor. Cytologic examination of the mass over the right eye was suggestive of a mast cell tumor. The dog was neutered, the oral melanoma was removed and the mast cell tumor removed from over the eye. Histopathology confirmed the diagnoses as mast cell tumor and interstitial cell tumor. The dog was treated with bacillus calmette-guerin (BCG; a nonspecific immunomodulator that actively stimulates the immune system to respond to a wide variety of substances that may harm the body, including

some cancers) given intralesionally and two doses of cisplatin. The dog never attained remission and died due to metastases and continual tumor growth.

CASE 16: Canine Maxillary Melanoma

A 4-year-old, castrated male, 91-pound mixed breed dog was presented for a mass behind the left upper canine, which the owner noticed 2 weeks earlier. The mass was biopsied at the referring veterinarian and diagnosed as melanoma. An eroded mass was found on the ventral surface of the gingiva. Serum biochemistry revealed increased ALP (980) and ALT (740). No other abnormalities were present. An MRI showed left-sided rostral maxillary mass extending from the canine through the second premolar, invading partially through the corner of the nasal cavity and infiltrating somewhat into the nasal turbinates, but the mass remained well marginated. A hemimaxillectomy and mandibular lymph node excision was completed. Histological examination was diagnostic of an amelanotic melanoma in the maxilla and pyogranulomatous inflammation in the lymph nodes. The dog was still in remission 15 months after surgery.

CASE 17: Canine Lung Tumor

A 13-year-old, spayed female, 33.5-pound cocker spaniel presented with a chronic cough of 3 weeks and a mass in the cranial left dorsal lung lobe. The right front mammary gland had been removed 16 months earlier. Several small masses were found on examination: a 10 × 5 cm mass on the left lateral abdominal wall, and a pea-sized mass in the right third mammary gland. A cough was elicited, and harsh lung sounds were heard on both sides of the lungs. All laboratory findings were within normal limits. Thoracic radiographs revealed a mass associated with the left cranial main stem bronchus with possible extension to the hilar region or extension to the hilar lymph nodes (Figure C17-1). A diffuse increased bronchial pattern was observed.

Cytologic evaluation of a fine-needle aspirate of the thoracic mass was suggestive of carcinoma, possibly bronchiolar alveolar in origin. The dog was given Adriamycin therapy once every 3 weeks for a total of three doses. However, the dog died at home 1 month after completion of the therapy.

Key Points

Originally, the lung mass was believed to be metastatic mammary carcinoma. Histologic examination proved the dog to have a new malignancy. Tumors of the respiratory tract are uncommon in dogs. The most common

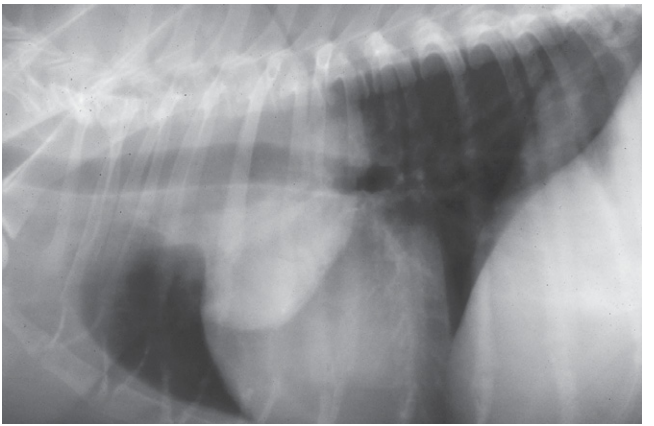

Figure C17-1 This and other survey radiographs suggested a primary bronchial alveolar carcinoma with mass extension to the hilus or metastasis to regional lymph nodes and possibly throughout the chest.

clinical signs in dogs with lung tumors are weakness, lethargy, weight loss, not coughing or wheezing. Most lung tumors are observed unexpectedly after taking routine thoracic images. Lung tumors tend to be solitary masses affecting the caudal lung lobes (right more than left) more than the cranial lung lobes; pleural effusion is uncommon. If associated tracheobronchial lymph nodes are not enlarged, the median survival of dogs is about 1 year following excision of a solitary lung tumor mass.

The survival is poor (<60 days) in dogs with poorly differentiated lung tumors or enlarged tracheobronchial lymph nodes.

CASE 18: Canine Hemangiopericytoma

A 10-year-old, castrated male, 62.5-pound German shepherd presented with a mass overlying the left carpus. The mass had been removed twice and grown back rapidly. There was firm, ulcerated, lobulated, nonpainful mass on mediolateral aspect of the left carpus (Figure C18-1). A fine-needle aspiration biopsy of the mass was performed (Figure C18-2). No evidence of pulmonary metastasis was seen on survey thoracic radiographs, and an incisional biopsy was obtained (Figure C18-3).

The tumor and approximately 4 cm of surrounding normal tissue on the left distal antebrachium were

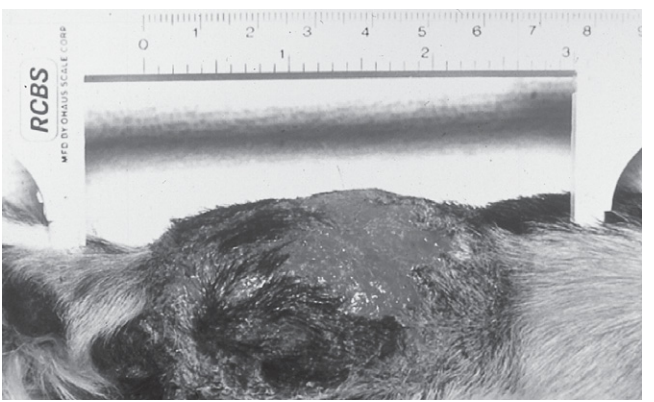

Figure C18-1 Carpal mass in a German shepherd.

exposed to a combination of radiation and hyperthermia. The tumor mass decreased in overall size by >50% over the 6-week treatment period (Figure C18-4).

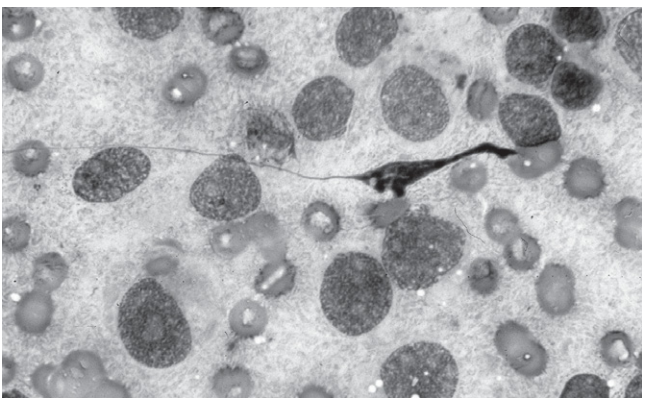

Figure C18-2 Cytologic examination showed a uniform population of pleomorphic mesenchymal cells with indistinct cytoplasmic borders, suggestive of a fibrosarcoma or hemangiopericytoma.

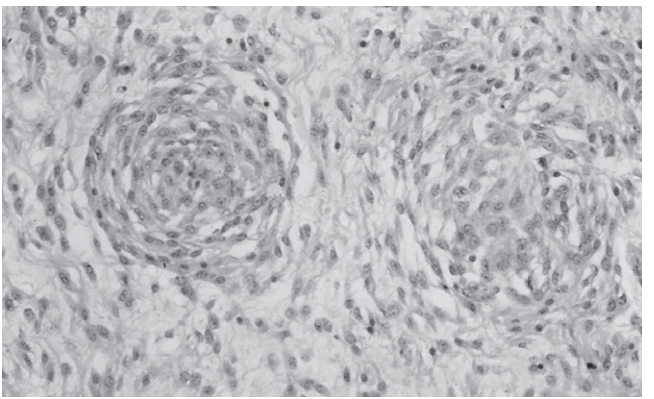

Figure C18-3 Histological findings were consistent with a diagnosis of hemangiopericytoma. Note the typical whorled pattern of mesenchymal tumor cells observed in canine hemangiopericytomas.

Figure C18-4 Two months following the completion of radiation therapy, the hemangiopericytoma was smaller in size. The dog was able to enjoy full function of the limb. No further progression in size of the tumor was noted after more than 2 years.

CASE 19: Canine Hepatic Carcinoma

A 9-year-old, spayed female, 36-pound mixed breed dog was referred because of a mass in the right cranial abdomen. The dog had a history of mast cell tumor removal from the neck 2 years ago and basal cell tumor removal from the neck 1 year ago. A large soft mass on the cranial thorax was palpated. Also palpated was a large firm mass in the cranial abdomen. The abdominal mass seemed to have the right kidney associated with it. The inguinal lymph nodes were enlarged. A CBC showed decreased RBC and PCV and an increased WBC (25.2) count. Also, 3 nucleated RBC per 100 WBC were noted. Serum biochemistry revealed increased ALP (2840), ALT (2370), and aspartate transaminase (AST; 4420). Ultrasonic evaluation showed a right-sided hepatic mass with secondary masses in the remaining hepatic parenchyma. The right kidney was seen to be displaced by the mass but not involved.

The mass was removed and the section examined histologically. It was diagnosed as hepatocellular carcinoma. The dog was treated with Adriamycin four times. Remarkably, the dog was still alive 3 years following diagnosis.

CASE 20: Feline Nasal Plane Squamous Cell Carcinoma

A 10-year-old, intact female, 11-pound domestic shorthair cat presented with a 3-month history of an erosive lesion on the rostral aspect of the nasal plane (Figure C20-1). A topical antimicrobial ointment had been applied previously with no apparent effect. An erosive mass encompassing the left nares extending onto the nasal plane was observed. The remainder of the physical examination was normal. Using a scalpel blade, the lesion was gently scraped and the cells smeared onto a microscope slide for cytologic evaluation (Figure C20-2). Histologic examination of a superficial pinch biopsy confirmed a diagnosis of squamous cell carcinoma. Photodynamic therapy (PDT) was used to treat the rostral nasal plane of this cat. A circumferential necrotic lesion formed over 24 hours and the granulated wound reepithelialized over the next 6 weeks.

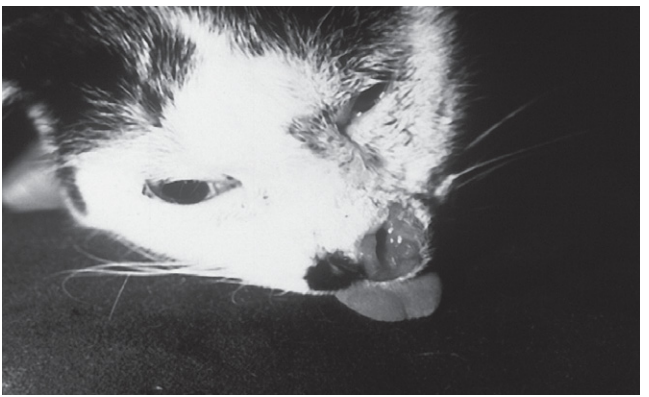

Figure C20-1 An erosive mass on the nasal plane of a cat.

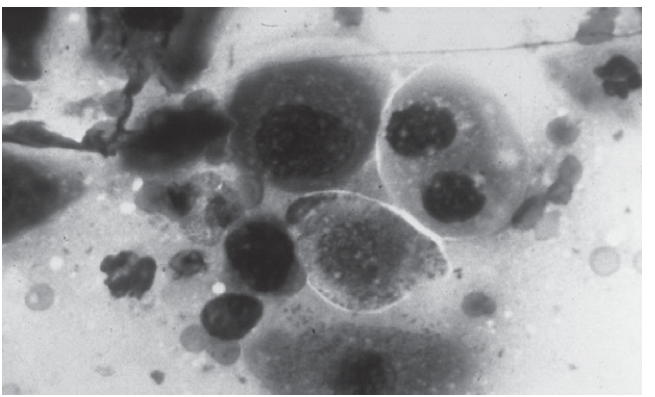

Figure C20-2 Squamous cell carcinoma as observed on a cytologic smear of cells obtained by scraping the nasal plane lesion with a scalpel blade.

CASE 21: Canine Nasal Adenocarcinoma

A 13-year-old, intact male, 18-pound miniature poodle presented with a nasal adenocarcinoma diagnosed by the referring veterinarian. The carcinoma started in the left nostril and crossed the septum to the right nostril. A 5-month history of occasional epistaxis was noted. A grade IV holosystolic left apical murmur and external facial asymmetry were noted. The following laboratory findings were abnormal: BUN (26), creatinine (1.4), ALP (285). The CBC was within normal limits. Magnetic resonance images of the skull showed an aggressive lesion in the left nasal passage compatible with neoplasia (Figure C21-1).

Multiple pieces of nasal mucosa were cytologically examined and a diagnosis of carcinoma was confirmed. A rhinotomy followed by the placement of iridium implants in the nasal sinuses for 4 days (radiation therapy) was performed. An additional 10 treatments with external beam irradiation to the ethmoid region of the nasal cavity was performed. The dog was alive 3.5 years after the surgery and radiation procedures.

Key Points

Tumors of the respiratory tract are uncommon in dogs. Tumors of the nasal and paranasal sinuses are the most common respiratory tract malignancies. The most common clinical signs are epistaxis and sneezing. Metastatic

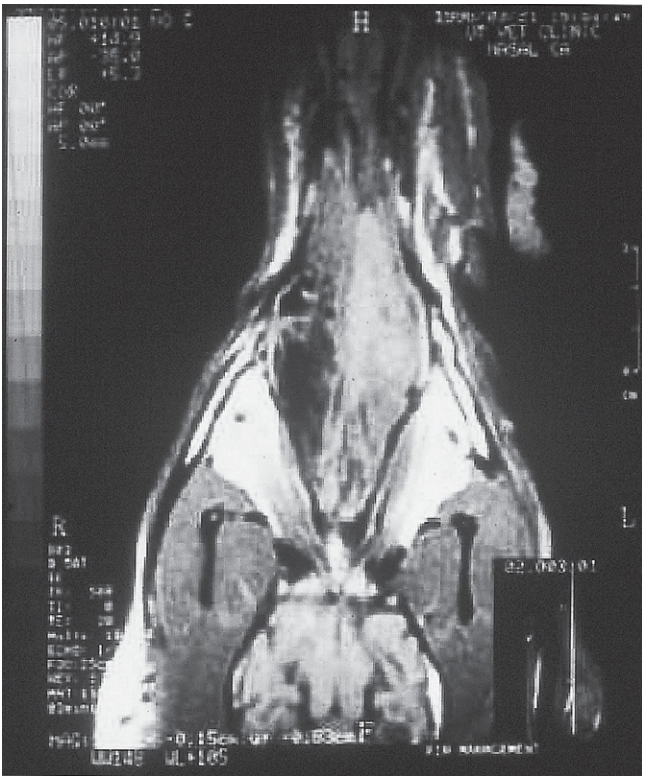

Figure C21-1 MRI scan of the nasal passages of a dog. Note the increased soft tissue density along the left side.

disease is uncommon; however, a thorough examination of the head, neck, and thorax should be performed. The lifespan of a dog with a nasal malignancy is greatly prolonged following localized radiation therapy to the entire nasal and frontal sinus regions of the head, generally 18–24 months with external beam radiation therapy protocols and 36–48 months following brachytherapy (implant radiation) protocols. Surgery without adjuvant radiation is not recommended; the survival of these dogs is generally <6 months. The survival time is shorter in dogs with mesenchymal nasal tumors (chondrosarcomas), generally 12–15 months.

Recommended Reading

In addition to the guiding principle of "biopsy, biopsy, biopsy," always consider the corollary "when in doubt, check it out." Keep current on information published in peer-reviewed scientific journals, comprehensive internal medicine textbooks, and always seek the advice of a veterinary oncologist. The resources in print that I find helpful on a regular basis in my clinic and used as the sole reference materials for this book are these:

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