Veterinary Surgical Oncology

Edited by Simon T. Kudnig and Bernard Séguin

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To my wife Narelle, my parents Philip and Judy, my brother Martin, and my sister Mandy for their unending support and understanding, and to my daughter Samantha for the joy and perspective on life you have brought.
S.K.

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B.S.

To Dr. Stephen J. Withrow for teaching us, among many other things: "Success is the ability to move forward in the face of failure."
S.K. and B.S.

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Preface

This book is the result of the collaboration between many contributors who belong to the Veterinary Society of Surgical Oncology (VSSO). At its inception, the impetus to write this book was to help fulfill the goals of the VSSO, which include "to disseminate knowledge to help provide the highest possible standard of surgical treatment for cancer and to encourage and promote education in surgical oncology for professional veterinary students, graduate students and house officers, and graduated veterinarians and veterinary surgeons" (www.vsso.org/aims.html).

The field of surgical oncology has greatly expanded in recent years. The creation of the VSSO reflects this growth. The idea of the VSSO was the brainchild of Dr. Steve Withrow. Dr. Withrow is, for many of us, the pioneer of surgical oncology in veterinary medicine, and he instituted the first fellowship in veterinary surgical oncology in 1988. Many of the original members of the VSSO are graduates of the fellowship. Under the leadership of Dr. Julius Liptak, the VSSO was officially created in 2006. In the first year of the VSSO, there were less than 30 members, whereas at the time of publication there are more than 235. Members are from North America, Europe and the United Kingdom, Australia and New Zealand, and Asia.

The American College of Veterinary Surgeons (ACVS) has announced that it will recognize further training and expertise in certain fields of surgery, one of which is oncologic surgery. This is affirmation of the expanding body of knowledge in surgery in general as well as that focusing on a certain field is necessary to remain the most proficient. The recognition of advanced training in a field will best promote continued development of novel ideas that will increase our understanding of the diseases and their treatment. We hope this textbook will serve as a repository of knowledge for anyone with an interest in surgical oncology to use and to build upon in the future.

The emphasis of this book is on the surgical aspect of treating small animals afflicted by cancer. This book is not meant to be a full review of small animal oncology as there are several excellent existing textbooks doing so. For instance, this book was not meant to be a comprehensive review of how to diagnose the diseases. Rather, we wanted to concentrate on the surgical procedures, such as those that are not well covered in the literature. Our goal is to assist decision making and to cover controversies in the field. The reader is expected to have a basic knowledge of general surgical principles and surgical techniques.

We are indebted to all the contributors for their remarkable contributions. The excellence of the chapters is to their credit and not ours, but any errors are our responsibility. We want to thank Erin Gardner, Erica Judisch, Nancy Turner, Erin Magnani and Susan Engelken from Wiley-Blackwell for their assistance and patience during this whole process, which was for the most part new to both of us. We also want to thank Jane Loftus for copy-editing the chapters; and Dave Johnson and Lorie Kennerly from the Information Technology Services at the College of Veterinary Medicine, Oregon State University, for their assistance when needed. We also thank Jill Bartlett from Oregon State University and Jean-François Séguin for their technical assistance with some of the figures. We need to thank our colleagues, house officers, students, and staff for their support and the motivation they supplied. And most importantly, we thank our families who by extension and default have lived through the creation of this book. Without their support and understanding, this would not have been possible.

We hope you find this book helpful in your practice and education and welcome any comments you may have.

Simon T. Kudnig and Bernard Séguin

Veterinary Surgical Oncology

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Principles of surgical oncology

Nicole Ehrhart, William T.N. Culp

Cancer treatment is a rapidly changing and evolving area involving the use of multiple diagnostic and therapeutic modalities to achieve the most optimal outcome. Surgical intervention remains a pivotal aspect of the treatment of cancer. Surgery cures more cancer than any other single modality. Nonetheless, the optimal treatment pathway for any given animal patient with cancer most often involves several adjuvant treatment modalities. Adjuvant treatments significantly affect the success of surgery, and likewise, surgery affects the outcome of adjuvant treatments. It is widely recognized in human cancer centers that patient outcome is greatly improved when surgery is performed by a surgeon with specialized training in oncologic procedures. These surgeons have expertise in selecting surgical treatment options in combination with other forms of cancer treatment, as well as knowledge of the benefits and risks associated with a multidisciplinary approach beyond that which can be mastered within a 3-year surgery residency training program. This level of expertise requires an understanding of the fundamental biology of cancer, clinical pharmacology, tumor immunology and endocrinology, as well as a thorough understanding of potential complications of multimodality therapy. Veterinary training programs in surgical oncology have been in existence for the last 14 years. With the development of new treatments such as small molecule inhibitors, gene therapy, and new forms of radiation, the role of the surgical oncologist is constantly evolving and changing (O'Reilly et al. 1997; Drixler et al. 2000).

Therapeutic goals (e.g., curative intent, cytoreduction, or palliation) for each case should be established with the pet owners before surgery is initiated. The efficacy of surgical therapy in any patient with cancer is heavily dependent upon the surgeon's global understanding of the patient's general health status, lifestyle, and activity level; type and stage of cancer; adjuvant therapies available; alternatives to surgery; and expected prognosis. To maximize effectiveness, the optimal treatment pathway for each case should be strategically assessed before initiating treatment. This planning should always include a frank and thorough discussion with the owner regarding preoperative diagnostic tests, stage of cancer, palliative options, surgical options, adjuvant treatments likely to be needed, costs, postoperative care, and expected function, cosmesis and prognosis including risks of complications. The goal of this discussion is to provide owners with enough information to help them make an informed choice regarding the best treatment plan for their companion. Highly individualized initial planning will allow for the best overall outcome for each patient.

Preoperative Considerations

Signalment

The patient's age, gender, breed, and weight are important factors in the determination of appropriate recommendations. Advanced age is not necessarily a negative prognostic factor. Comorbidities common to geriatric veterinary patients such as renal insufficiency, hepatic disease, or osteoarthritis may limit or change specific treatment recommendations; however, the age of the patient alone should not.

Certain neoplastic diseases are common in a particular gender or breed. The surgical oncologist should always bear in mind the role that gender and breed play in the diagnosis of neoplasia. As an example, the differential list for a flat-coated retriever with a femoral bony lesion noted on radiographs that has been referred

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for a suspected diagnosis of osteosarcoma should be expanded to include histiocytic sarcoma; other diagnostics such as an abdominal ultrasound would be recommended to look for other foci of histiocytic disease.

Other portions of the signalment are also important to note, including the patient's weight and body condition. Patients that are morbidly obese or those in poor body condition may not be able to function effectively or may be more severely debilitated by a major surgery. For example, a patient with cancer cachexia can have such profound alterations of their carbohydrate, protein, and fat metabolism that recovery may be compromised (Ogilvie 1998).

Staging and concomitant disease

Staging diagnostics such as a complete blood count, chemistry profile, urinalysis, thoracic radiographs, and abdominal ultrasound are essential components for the preoperative assessment of veterinary oncology patients. While there is debate about the timing of some of these diagnostics (i.e., before or after biopsy), for many patients thorough preoperative staging diagnostics can unmask an underlying condition that may alter the plan or better assist the surgeon to provide a more accurate prognosis. Alternative surgical dose may also be recommended based on the results of staging.

Neoadjuvant therapy

The surgical oncologist is often presented with extremely large tumors or tumors located in difficult anatomical locations. It is important to consider neoadjuvant treatments, if available and warranted, such as chemotherapy and radiotherapy before proceeding with surgery. In some cases, these treatments may decrease the overall surgical dose needed to achieve local control. Most commonly, recommendations about chemotherapy and radiation therapy are made after the grade of the tumor and the surgical margins have been determined. In tumors that are suspected to be sensitive to chemotherapy based on published literature or previous experience, a postoperative protocol can be discussed prior to surgery.

Neoadjuvant chemotherapy is rarely pursued in veterinary medicine. However, for certain tumor types, this may prove to be a beneficial adjunct to surgery. In human cases of osteosarcoma, neoadjuvant chemotherapy is commonly used prior to surgery and local tumor response (as measured by percentage of tumor necrosis) has been shown to be associated with increased survival. A recent veterinary study showed that neoadjuvant chemotherapy with prednisone administered to a group of dogs with intermediate grade mast cell tumors resulted in tumor size reduction; surgical excision of very large mast cell tumors or tumors that were in an anatomical site that precluded wide (3 cm lateral and one facial plane deep) excision was more successful (Stanclift and Gilson 2008). Microscopically complete margins were achieved in many of the pretreated cases. These patients would not likely have had complete surgical margins otherwise (Stanclift and Gilson 2008). Long-term follow-up was not the focus of this study, however, and controversy exists as to the risk of local recurrence in patients where neoadjuvant chemotherapy is used to shrink gross tumor volume to allow a less aggressive surgical margin. Further study is needed to assess the benefit of neoadjuvant chemotherapy in veterinary cancer patients.

Neoadjuvant radiation therapy has also been advocated as a method of treating neoplastic disease to reduce the need for radical surgery (McEntee 2006). Advantages to neoadjuvant radiation therapy include a smaller radiation field, intact tissue planes, better tissue oxygenation, and a reduction in the number of viable neoplastic cells that may be left within a postoperative seroma or hematoma following microscopically incomplete margins. Complications such as poor wound healing may occur more commonly in irradiated surgical sites than in nonirradiated tissue due to the effects of radiation on fibroblasts and blood vessels (Séguin et al. 2005). Even so, surgery in previously irradiated fields can be quite successful provided care is taken to ensure minimum tension, careful surgical technique, and appropriate timing (either before or after acute effects have occurred). Consultation with a radiation oncologist prior to surgery can help the surgeon identify those patients who may be good candidates. Considerations such as whether or not preoperative radiation will diminish the surgical dose and what type of reconstruction will be needed to ensure a tension-free closure in an irradiated surgical field should be discussed at length prior to deciding if neoadjuvant radiation is warranted.

Surgical Planning

Fine-needle aspirate

Fine-needle aspiration is often the most minimally invasive technique for obtaining critical information about a newly identified mass prior to surgery. The accuracy of a fine-needle aspirate depends on many factors, including the tumor type, location, and amount of inflammation. Overall sensitivity and specificity of cytology has been reported to be 89% and 100%, respectively (Eich et al. 2000; Cohen et al. 2003). Imaging tools such as ultrasound and fluoroscopy can increase the chance of obtaining a diagnostic sample.

In most patients, a fine-needle aspirate of cutaneous or subcutaneous lesions can be obtained with no sedation and a minimal amount of discomfort. Fine-needle aspiration has been compared to histopathological samples in several studies. In a recent study of the correlation between cytology generated from fine-needle aspiration and histopathology in cutaneous and subcutaneous masses, the diagnosis was in agreement in close to 91% of cases (Ghisleni et al. 2006). Cytology was 89% sensitive and 98% specific for diagnosing neoplasia (Ghisleni et al. 2006). The goal of fine-needle aspiration is to differentiate between an inflammatory or neoplastic process, and if neoplastic, whether the tumor is benign or malignant. In some cases, the specific tumor type can be determined (e.g., mast cell tumor). In other cases, the class of tumor may be identified (e.g., sarcoma), but the specific diagnosis requires histopathology (e.g., chondrosarcoma versus osteosarcoma). The overall purpose of performing the fine-needle aspiration is to guide the staging diagnostics (where to look for metastasis or paraneoplastic diseases) and surgical dose. For example, a fine-needle aspirate of a mass showing normal adipocytes would indicate that the mass is not inflammatory; rather, it is a neoplastic process and is benign (lipoma). Based on the knowledge of the biological behavior of this tumor we would perform no other staging tests and prescribe a minimal surgical dose (marginal resection). Alternatively, if the fine-needle aspirate of a mass indicated carcinoma cells, we would be prompted to perform more advanced staging (three-view thoracic radiographs, abdominal ultrasound, lymph node aspirates) and would prescribe a larger surgical dose.

Fine-needle aspiration of internal organs can also be performed and may be helpful in guiding diagnostic and treatment choices. Image guidance should be used when obtaining tissue from fine-needle aspirations of masses within a body cavity. Aspirates of lung and other thoracic organs can be performed safely in most cases. In one study, fine-needle aspiration of lung masses had a sensitivity of 77% and a specificity of 100% (DeBerry et al. 2002). The aspiration of cranial mediastinal masses is beneficial, as thymomas can be diagnosed by cytology (Rae et al. 1989; Atwater et al. 1994; Lana et al. 2006). Cytological diagnosis of thymoma requires the presence of a population of unequivocal malignant epithelial cells. The presence of mast cells is also common in thymoma and often supports the diagnosis (Atwater et al. 1994). Flow cytometry is another diagnostic tool that will differentiate thymoma from lymphoma using a fine-needle aspirate sample. Thymomas will contain both CD4+ and CD8+ lymphoctyes, whereas lymphoma would typically contain a clonal expansion of one lymphocyte type (Lana et al. 2006).

Fine-needle aspiration of hepatic and splenic neoplasia has been described in several studies (Osborne et al. 1974; Hanson et al. 2001; Roth 2001; Wang et al. 2004). Successful diagnosis of hepatic neoplasia with fine-needle aspiration is variable. A study has reported diagnostic rates for liver cytology of multiple pathologies (including neoplasia) as high as 80% (Roth 2001); however, another study demonstrated less success with diagnostic rates of 14% in dogs and 33% in cats for fine-needle aspiration of hepatic neoplasia (Wang et al. 2004). In cases of suspected splenic hemangiosarcoma, fine-needle aspiration is generally not recommended, as an accurate diagnosis is unlikely due to the abundance of blood-filled cavities. Additionally, complications may include severe bleeding from the aspiration site. Fine-needle aspiration of splenic neoplasia such as lymphoma and mast cell tumors is often diagnostic (Hanson et al. 2001).

Other tumors in which fine-needle aspiration has been used to obtain diagnostic information include gastrointestinal tumors and bony tumors. The accuracy of fine-needle aspiration in the diagnosis of gastrointestinal neoplasia is often dependent on the type of neoplasia present. For instance, fine-needle aspiration of gastrointestinal lymphoma tends to have a higher sensitivity than aspiration of gastrointestinal carcinoma/adenocarcinoma or leiomyoma/leiomyosarcoma (Bonfanti et al. 2006). The specificity of the diagnosis is similar among these neoplastic diseases with fine-needle aspiration (Bonfanti et al. 2006). In a recent report, ultrasound-guided fine-needle aspiration of osteosarcoma lesions was found to have a sensitivity of 97% and specificity of 100% for the diagnosis of a sarcoma (Britt et al. 2007). Another study found that cytology after fine-needle aspiration agreed with incisional and excisional biopsies of bony lesions in 71% of cases (Berzina et al. 2008).

As with any procedure, fine-needle aspirates are not without risk. In certain cases, bleeding or fluid leakage can be problematic, especially within a closed body cavity where it cannot be easily controlled. Tumor seeding and implantation along the needle tract is a rare occurrence but in certain tumors has been reported more frequently. Localized tumor implantation following ultrasound-guided fine-needle aspiration of transitional cell carcinoma of the bladder has been reported (Nyland et al. 2002) and should be a consideration when deciding on methods for diagnosing bladder masses. Fine-needle aspiration of mast cell tumors can cause massive degranulation, and clinicians should be prepared to treat untoward systemic effects following aspiration of a suspicious or known mast cell tumor. Despite the risks associated with fine-needle aspiration,

it remains an effective, inexpensive, and valuable tool in the preoperative planning process.

Biopsy

Clinicians often use the term *biopsy* as a nonspecific description of obtaining a tissue sample for histopathological interpretation. For this reason, we will designate biopsy procedures into two major categories: pretreatment biopsy (tissue obtained before treatment initiation) or posttreatment biopsy (tissue obtained at the time of definitive tumor resection). We will also give examples of specific biopsy techniques. All biopsy procedures, whether pretreatment or posttreatment, should be carefully planned with several factors in mind. These factors include known patient comorbidities, anatomical location of the mass, differential diagnoses, biopsy technique, eventual definitive treatment, and any neoadjuvant or adjuvant therapies that may need to be incorporated.

Pretreatment biopsy

Needle core biopsy

This technique is commonly used for soft tissue, visceral, and thoracic masses (Osborne et al. 1974; Atwater et al. 1994; deRycke et al. 1999). Image guidance is recommended when using this technique in closed body cavities. Most patients require sedation and local anesthesia but do not need general anesthesia.

Instrumentation includes a needle core biopsy instrument (automated or manual), no. 11 scalpel blade, local anesthetic, and a 22-gauge hypodermic needle. To perform the procedure, the area surrounding the mass is clipped free of fur and prepared with aseptic technique. If intact skin is to be penetrated and the animal is not anesthetized, the skin overlying the area to be penetrated is anesthetized with lidocaine or bupivicaine. A 1–2 mm stab incision is made over the mass to allow for placement of the needle core biopsy instrument. The instrument is oriented properly and fired, and the instrument is withdrawn. The 22-gauge needle can be used to gently remove the biopsy from the trough of the needle core instrument. This identical procedure is performed for masses within a body cavity; however, it is necessary to use image guidance for proper placement of the instrument within the desired tissue. Imaging can be used to determine the depth of penetration and to safely avoid nearby vital structures.

Punch biopsy

The punch biopsy technique is most effective for cutaneous lesions as well as intraoperatively for biopsies of masses within organs such as the liver, spleen, and kidney. Subcutaneous lesions can be biopsied using this method, but it is best to incise the skin overlying the mass and then obtain the sample using the biopsy instrument.

Instrumentation includes a punch biopsy instrument, no. 11 scalpel blade, local anesthetic, Metzenbaum scissors, forceps, and suture. The area containing the mass is clipped free of fur and prepared with aseptic technique. If intact skin will be penetrated and the animal is not anesthetized, the skin overlying the lesion is anesthetized with lidocaine or bupivicaine. For cutaneous masses, an incision is not necessary. For subcutaneous masses, make an incision in the skin over the mass to allow a better sample to be procured. The skin incision should be large enough for the punch biopsy instrument to be placed and allow it to be twisted without engaging skin. Twist the punch biopsy instrument until the device is embedded into the mass to the hub. The punch biopsy instrument is then withdrawn from the mass to expose the tissue sample. Gently grasp the sample with forceps, use Metzenbaum scissors to sever the deep aspect of the sample from the rest of the tissue, and remove the sample. A single suture is generally sufficient to close the incision. The same procedure can be performed on visceral organs.

Incisional (wedge) biopsy

The incisional biopsy technique is effective for masses in all locations and generates a larger sample for histopathological evaluation as compared to the needle core biopsy. The location of the incision should be carefully planned, as the biopsy incision will need to be removed during the definitive treatment. Care should be taken to avoid dissection and prevent hematoma or seroma formation as these may potentially seed tumor cells into the adjacent subcutaneous space. Although the junction of normal and abnormal tissue is often mentioned as the ideal place to obtain a biopsy sample, one should take care to avoid entering uninvolved tissues. Obtaining a representative sample of the mass is the most important principle to consider. It is also important to obtain a sample that is deep enough and that contains the actual tumor, rather than just the fibrous capsule surrounding the mass. Incisional biopsy has a higher potential for complications such as bleeding, swelling, and infection due to the increase in incision size and dissection.

Instrumentation includes a no. 11 or no. 15 scalpel blade, local anesthetic, Metzenbaum scissors, forceps, suture, and hemostats. A gelpi retractor or similar self-retaining retractor aids in visualization if the mass is covered by skin. If the skin is intact and moveable over the mass, a single incision is made in the skin. Once the tissue layer containing the tumor is exposed, two parallel

incisions are started superficially and then meet at a deep location to form a wedge. The wedge is then grasped with forceps and removed. If the deep margin of the wedge is still attached, the Metzenbaum scissors can be used to sever the biopsy sample free of the parent tumor. The wedge site is then closed with suture.

Posttreatment biopsy (excisional biopsy)

The approach to an excisional biopsy varies based on location, goal of surgery, and predetermined adjuvant therapy. An excisional biopsy has the advantage of being both a diagnostic technique as well as a treatment modality. A great deal of caution should be exercised in cases where the diagnosis is unclear. At a minimum, a fine-needle aspirate should be obtained to discern if a given mass is inflammatory or neoplastic, and if neoplastic, whether benign or malignant. This information is imperative in order to determine surgical dose.

There are cases where an excisional biopsy may be a reasonable option if doubt remains after fine-needle aspiration, depending on the size and location of the tumor. In these instances, the surgeon must contemplate if an excisional biopsy will compromise the ability to enact a cure by using a wide excision. If it is deemed that an excisional biopsy can be performed while leaving this option, an excisional biopsy may be considered.

Once an excision is performed, the local anatomy is forever altered; both deep and wide tissue planes to the tumor are invaded, providing the opportunity for tumor cells to extend and seed deeper and wider into tissues. For this reason, the best chance for complete excision is at the time of the first surgical excision. In order to perform a curative surgery, the surgeon must take the appropriate margin of tissue for the tumor type. In some cases (e.g., lipoma), this margin is minimal or even intralesional. In other cases (e.g., soft tissue sarcoma), the margin should be much more extensive. Unless the tumor type is known at the time of excision, the surgeon may compromise the patient by doing too little or too much surgery.

Specific biopsy techniques

Bone biopsy

The clinician performing the bone biopsy procedure should consider the eventual definitive treatment that is likely to be pursued for each case. The biopsy tract or incision needs to be in a location that can be removed during the definitive treatment. A reactive zone of bone exists in the periphery of most bone tumors, and samples taken from this region are more likely to result in an incorrect diagnosis (Wykes et al. 1985; Liptak et al. 2004). The surgeon should target the anatomical center of the bony lesion. Two radiographic views of the involved bone should be available during the procedure as this will aid in optimal sampling. The majority of bone biopsies are performed using either a Michele trephine or a Jamshidi needle (Wykes et al. 1985; Powers et al. 1988; Liptak et al. 2004). A trephine instrument provides a large sample and has been associated with 93.8% diagnostic accuracy (Wykes et al. 1985). The disadvantages of the trephine technique include increased likelihood of fracture as compared to other techniques, requirement of a surgical approach, and a more lengthy decalcification time prior to sectioning (Wykes et al. 1985; Ehrhart 1998).

Michele trephines are available in variable diameters. As a small surgical approach is required, a simple surgical pack is needed for the procedure. The biopsy site is clipped free of fur, and the patient is prepared with aseptic technique and draped. A 1–3 cm incision is made over the bony lesion, and the soft tissues are dissected from the surface of the tumor. The trephine is then seated into the tumor using a twisting motion. The trephine is advanced through the cis cortex. An effort should be made to not penetrate both the cis and trans cortex as fracture of the bone is more likely (Liptak et al. 2004). Once the trephine is within the medullary cavity, the trephine is rocked backed and forth to loosen the sample and then removed. A stylet is introduced into the trephine to push the sample out of the trephine onto a gauze square.

The Jamshidi needle technique is considered a less invasive means of obtaining a bone biopsy as compared to a Michele trephine. A small stab incision is necessary to introduce this device and fractures are unlikely. In approximately 92% of cases, a correct diagnosis of tumor versus nontumor is achieved when using a Jamshidi needle (Powers et al. 1988).

Instrumentation includes a no. 11 scalpel blade and a Jamshidi needle. The surgical site is clipped free of fur, and the patient is prepared with aseptic technique and draped. A 1–2 mm stab incision is made over the bony lesion. The Jamshidi needle is introduced into the stab incision and pressed onto the bony lesion. The stylet is then removed from the needle, and the needle is twisted until the cis cortex is penetrated. The Jamshidi needle is rocked back and forth to loosen the sample and then removed. The stylet is reintroduced into the needle in the opposite direction of the initial location. As the stylet is moved through the Jamshidi needle, the biopsy will be ejected from the base of the Jamshidi needle.

Lymph node biopsy

Treatment and biopsy of lymph nodes in neoplastic disease remains controversial (Gilson 1995). Removing

a lymph node or performing an incisional biopsy of a lymph node can aid in staging the patient and assist in determining prognosis or treatment options. The surgical oncologist should have a thorough knowledge of the anatomical location of the probable draining lymph node for a mass in a particular location. The excisional biopsy of superficial lymph nodes such as the mandibular, prescapular, axillary, inguinal, or popliteal lymph nodes is described below. For removal of lymph nodes within the thorax or abdomen, an exploration of that body cavity is performed, and the lymph nodes are removed by careful dissection and maintenance of hemostasis.

Instrumentation includes a no. 10 or no. 15 scalpel blade, Metzenbaum scissors, forceps, suture, and suture scissors. The surgical site is clipped free of fur, and the patient is prepared with aseptic technique and draped. An incision slightly larger than the palpable lymph node is made parallel to the axis of the lymph node. The superficial tissue overlying the lymph node is bluntly and sharply dissected. The lymph node capsule is then grasped with the forceps and blunt or sharp dissection is performed around the lymph node to free it from the surrounding tissue. Vessels that are encountered may need to be ligated. The lymph node is then removed, and the subcutaneous tissue and skin are closed.

Endoscopic biopsy

Esophagoscopy, gastroscopy, duodenoscopy, and colonoscopy are routinely performed in veterinary medicine as minimally invasive techniques to attain biopsy tissue from the gastrointestinal tract. Biopsies attained during these procedures are generally smaller than that which can be achieved with an open procedure; however, the biopsies are often diagnostic, and the morbidity associated with these procedures is reduced over open procedures (Magne 1995; Moore 2003).

Laparoscopy and thoracoscopy are still relatively underused modalities, but successful procurement of kidney, bladder, liver, spleen, adrenal gland, pancreas, stomach, intestine, and lung biopsies have been described by use of these procedures (Rawlings et al. 2002; Lansdowne et al. 2005; Vaden 2005; Barnes et al. 2006). Case selection is essential when considering these minimally invasive alternatives, as cases that have excessively large tumors or other potential contraindications should undergo an open procedure.

Laparoscopy and thoracoscopy may have a role in the staging of veterinary patients as the use of these techniques increases. In cases where lymph node evaluation and biopsy would assist in predicting outcome or determining treatment, these procedures could be performed by minimally invasive techniques (Fagotti et al. 2007).

Surgical considerations for curative-intent surgery

Certain surgical technical principles will improve the chance of success and minimize the risk of local or distant seeding of tumor cells. The tumor should be draped off from the rest of the surgical field. Surgeons should avoid contact with ulcerated or open areas of tumor with gloves or instruments. Sharp dissection is preferred over blunt dissection when possible, as this will decrease the likelihood of leaving neoplastic cells within the patient and decrease the risk of straying from the preestablished margin. Tension on skin closures should be avoided whenever possible, especially in cases that have undergone radiotherapy. Proper knowledge of tension-relieving techniques such as tension-relieving sutures and flaps can assist in closure (Soderstrom and Gilson 1995; Aiken 2003). If an indwelling drain is deemed necessary in a tumor resection site, the drain should be located in an area that can be resected during a subsequent surgery or in an area that will not compromise radiation therapy and can easily be included in the radiation field. Lastly, control of hemostasis and prevention of seroma or abscess development due to dead space is encouraged. Seromas or hematomas following an incomplete resection allow tumor cells to gain access to areas beyond the surgical field as these fluids may be widely dispersed throughout the subcutaneous space during movement.

To decrease the risk of recurrence after tumor resection, there are several techniques the surgeon should practice. For tumors that have been previously biopsied or for which a drain has been placed, the biopsy tract and/or drain hole need to be removed en bloc with the tumor. Similarly, adhesions should be removed with the tumor, when possible. Leaving any of these can result in an increased risk of tumor recurrence. Additionally, when establishing a margin during surgical dissection, this margin must be maintained around the periphery of the tumor down to the deep margin. Straying from this may result in an incomplete resection. Similarly, the pseudocapsule present around a tumor should not be penetrated, as this pseudocapsule is constructed of a compressed layer of neoplastic cells (Soderstrom and Gilson 1995). Seeding of these cells will likely result in recurrence, and healing may be inhibited. Lastly, it is essential that a new set of instruments, gloves, and possibly drapes be used for closure of a wound created by tumor removal or reconstruction of a wound. This principle applies to the removal of subsequent tumors on the

same patient as these items should not be transferred from one surgical site to another.

Defining and evaluating surgical margins

The evaluation of surgical margins of an excised specimen is an essential component to appropriate care in a cancer patient. A surgical margin denotes a tissue plane established at the time of surgical excision, the tissue beyond which remains in the patient. Excised masses should be submitted in their entirety for evaluation of the completeness of excision. The surgeon should indicate the margins with ink or some other method prior to placing the specimen in formalin to aid the pathologist in identifying the actual surgical margin. Because the larger tumor specimen is trimmed by a technician to fit on a microscope slide, the pathologist may not be oriented as to what represents a surgical margin versus a sectioning "margin". Tissue ink on the surgical margin allows orientation throughout sectioning. The ink is present throughout the processing of the tumor specimen and is visible on the slide. If tumor cells are seen at the inked margin under the microscope, the surgical margin is by definition "dirty" or incomplete.

The surgical techniques used to remove tumors define the type and magnitude of intended surgical margin. When tumors are removed using an intracapsular technique, dissection occurs within the dimensions of the tumor and residual microscopic disease always remains (Soderstrom and Gilson 1995). Marginal excision refers to tumors excised with a 1 cm or less cuff of normal tissue surrounding the mass. Marginal excision may be quite appropriate for certain tumors such as lipomas but is often not sufficient for malignant tumors (Ehrhart and Powers 2007). Wide excision refers to tumors removed with 1–3 cm of normal tissue in all directions, including a deep margin. To achieve wide excision, the mass needs to be removed en bloc and the pseudocapsule and reactive zone should be completely contained within a cuff of normal tissue. Because dissection for a wide excision is intracompartmental, it is distinguished from a radical excision. A radical excision is considered an excision of normal tissue surrounding the mass of greater than 3 cm or the entire anatomical compartment (e.g., amputation). Extracompartmental excision is defined by a plane of excision beyond the anatomical compartment considered to have a cancer-resistant tissue barrier (Soderstrom and Gilson 1995).

Special focus is usually placed on mast cell tumors and soft tissue sarcomas when considering surgical margins. These tumor types generally have a bulky mass that is easily palpable; however, microscopic projections of tumor cells extend out from the main tumor bed (Séguin et al. 2001; Murphy et al. 2004; Ehrhart 2005). These tendrils of tumor cells need to be considered preoperatively so that a proper surgical dose can be determined. Historically, 3 cm margins were recommended for excision of mast cell tumors and soft tissue sarcomas. Recently, though, studies have shown that 2 cm margins are sufficient for complete excision of 91%–100% of grade 2 mast cell tumors (Simpson et al. 2004; Fulcher et al. 2006). Recommendations for surgical margins around soft tissue sarcomas, however, continue to be at least 3 cm (Aiken 2003; Ehrhart 2005; Liptak and Forrest 2007).

In many cases, the deep margin of a tumor excision can be less than 2–3 cm from the tumor if removal of one tissue plane deep to the last tissue plane the tumor touches is achieved. For example, if the tumor is freely moveable in the subcutaneous tissue of the thigh, removal of the fascia lata as the deep margin will often be sufficient to achieve a clean margin. On the other hand, if the tumor is attached to the fascia lata, a muscle plane deep to this layer must be removed to achieve a clean margin. Unfortunately, the true definition of a "fascial plane" is lacking in medicine, and specific guidelines remain elusive (Fasel et al. 2007). While to some authors the definition of fascia has included adipose tissue, this concept is not universally supported (Fasel et al. 2007). A current definition of fascia is considered "sheaths, sheets, or other dissectible connective tissue aggregations visible to the unaided eye" (Wendell-Smith 1997; Fasel et al. 2007). Furthermore, fascia can be "considered as gross structures enveloping and/or supporting other formations" (Fasel et al. 2007). These definitions support the removal of a deep layer of connective tissue (not including adipose tissue) when considering a deep margin.

When an incomplete margin is noted on histopathological evaluation, the surgeon must decide on the next appropriate course of action. Options include intensive monitoring for recurrence, reexcision, and chemotherapy and radiation therapy. Both human and veterinary studies support early reexcision of a surgical wound bed when an incomplete margin is achieved during the primary surgery (Raney et al. 1982; Gibbs et al. 1997; Bacon et al. 2007). The goal during a reexcision surgery is to achieve tumor-free margins. Therefore, the entire wound bed must be treated as a dirty site and must be completely removed with a margin of normal tissue around it so that all tumor cells and microscopic extensions previously left in the patient will be removed. This always requires a more extensive surgery than the original surgical attempt.

Palliative and cytoreductive surgery

The decision to perform a palliative or cytoreductive surgery is often a difficult one, and the surgeon needs to educate the client and referring veterinarian about the risks and benefits of such surgery. Piecemeal removal (debulking) of a mass should generally only be performed when the mass is physically causing obstruction or altering function. There is little advantage to debulking otherwise, unless the removal results in only microscopic amounts of disease left behind. Palliation of symptoms caused by obstructive masses by removing most of or portions of large masses can temporarily improve quality of life in some cases. This should be performed only when necessary as excessive bleeding can often occur and dehiscence is very common.

Postoperative Considerations

Tissue marking

As discussed above, following an excisional biopsy, the surgical margins of the mass should be clearly indicated in some way so that the histopathologist can accurately evaluate the mass for complete excision. Several methods have been proposed to do this, including specialized sectioning techniques, suture markers, inking, and the submission of adjacent tissue as a separate sample (Rochat et al. 1992; Mann and Pace 1993; Seitz et al. 1995). Inappropriate sectioning can result in neoplastic cells being noted at the cut margin, and a false-positive result can occur. Sutures can be used to mark a particular area of interest or for tumor orientation, but sutures need to be removed before sectioning to prevent microscopic artifact (Mann and Pace 1993). A sample of tissue surrounding the surgical wound can also be submitted for evaluation. However, this increases the size of the wound bed, and added expense may be seen due to the submission of extra biopsy samples.

In general, the marking of tumor margins with inks or dyes is recommended. Several types of inks and dyes have been evaluated, including merbromin, laundry bluing, India ink, alcian blue, typists' correction fluid, commercial acrylic pigments, and artists' pigment in acetone (Rochat et al. 1992; Mann and Pace 1993; Seitz et al. 1995; Chiam et al. 2003). Alcian blue has been shown to be the best marking material; however, india ink and commercial kits (Davidson Marking System, IMEB Inc., San Diego, CA) are reasonable alternatives (Seitz et al. 1995). One of the benefits of the commercial kits is that multiple colors are provided. When using these kits, all the margins can be marked in different colors, but at a minimum, the lateral margin can be marked in one color and the deep margin in a different color. Yellow, black, and blue are considered the best colors to use, whereas red and green are less ideal (Seitz et al. 1995).

Guidelines for fixation of surgical tissue specimens

Small biopsy samples should be placed in fixative immediately to prevent drying of the sample. Early fixation will initiate changes in the sample that will prevent autolysis and bacterial alteration of the sample (Stevens et al. 1974). In large biopsy submissions, the sample should be sliced evenly to allow more complete fixation (Dernell and Withrow 1998; Ehrhart and Withrow 2007). Many fixatives, including formalin, Bouin's fluid, chilled isopentane, Zenker's fluid, and glutaraldehyde have been described in veterinary medicine (Osborne 1974; Stevens et al. 1974), but in general, 10% buffered formalin is sufficient for almost all biopsies. A biopsy sample should be fixed in formalin in a 1:10 solution of tissue to formalin (Ehrhart and Withrow 2007).

Frozen sections

The use of frozen sections is common in human medicine. (Lessells and Simpson 1976; Kaufman et al. 1986). Frozen sections generate an accurate diagnosis in greater than 97% of human biopsy samples (Lessells and Simpson 1976; Kaufman et al. 1986). The process requires highly trained personnel and equipment specific to the procedure, and thus veterinary facilities that have the capability are limited (Ehrhart 1998). In one veterinary study, the accuracy of frozen sections in determining a specific diagnosis was 83% (Whitehair et al. 1993). In that same study, frozen sections were able to make a determination between neoplastic and non-neoplastic diseases in 93% of cases (Whitehair et al. 1993).

Wound healing

The veterinary oncology patient has several risk factors that may increase the frequency of complications associated with wound healing (Cornell and Waters 1995). Nutritional compromise and concomitant disease can be treated to improve the outcome of wound healing, but other factors such as tumor type and completeness of surgical excision have to be considered as well. Neoadjuvant and adjuvant therapies such as chemotherapy, radiotherapy, and antiangiogenic medications have also been documented to impair wound healing (Devereux et al. 1979; Cornell and Waters 1995; te Velde et al. 2002; Séguin et al. 2005).

Proper surgical technique as described above can be employed to decrease the chance of wound complications. Regular communication with the patient's owner

both before and after surgery will help to preemptively prepare for complications or aid in rapid identification and intervention when complications arise. Prevention of self-trauma should be routinely discussed with the owner, and methods of prevention such as bandaging or having the patient wear an Elizabethan collar should be included in the postoperative care.

Adjuvant therapy

The time to discuss the potential need for adjuvant therapy in a tumor patient is prior to any surgical intervention. This allows owners to make informed choices and to better prepare for the financial burden, time required, and potential complications associated with this type of therapy. Failing to properly prepare the client for these additional treatments and the benefits and challenges unique to each one may leave the patient's owner feeling overwhelmed, underinformed, and may expose the patient to unnecessary morbidity or delay in treatment.

Chemotherapy in the adjuvant setting is generally administered after wound healing has been completed. Experimentally, it has been shown that administering certain types of chemotherapy before or at the same time as surgery may retard wound healing (Shamberger et al. 1981; de Roy van Zuidewijn et al. 1986; Lawrence, Talbot et al. 1986; Lawrence, Norton, et al. 1986). By the time a patient is ready for suture or staple removal, a wound is generally healed sufficiently, and chemotherapy may be administered. The results of the biopsy will also be accessible at a similar time, and these can help to guide chemotherapeutic recommendations.

Radiation therapy may be administered preoperatively or postoperatively. In general, radiation therapy will slow wound healing. In cases where radiation is administered either before or after surgery, it is important to ensure that there is minimal tension on the wound closure. This requires careful planning prior to and during the initial surgery. In some cases, if local flaps require extensive dissection in areas away from the tumor bed and outside the proposed radiation field, it may be better to delay primary closure until it is known if tumor margins are clean. This will help prevent seeding of tumor cells along the dissection planes where the flap will be raised. In postoperative patients who require radiation therapy but have wound complications such as infection or dehiscence, it is often better to try to manage the wound complication before beginning radiation. This may not always be possible, as tumor remaining in the wound may prevent wound healing. In these cases, it may be necessary to go forward with radiation in an open wound setting. In many cases, once acute effects have resolved, the wound can be closed. In these cases, strict adherence to the "no skin tension" rule is imperative.

While certain basic concepts of surgery will remain static for the treatment of neoplasia, pursuit of better options for our patients will require that the surgical oncologist be able to adapt. It is hoped that the desire for improved outcomes will continue to improve the lives of our patients as well as their owners. Prolonging a quality of life for veterinary patients and advising their owners appropriately about the options that we have to offer should remain our goal as advances in therapy occur.

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2

Multimodal therapy

Tania A. Banks

The key to success for the effective management of many cancers in animals today and in the future lies in employing a multipronged attack. Multimodal therapy requires not only a sound understanding of the strengths and weaknesses of each modality used, the tumor's response to each treatment modality, and an accurate understanding of the various specific toxicities and interactions but also—and most importantly—a cooperative, communicative, interactive, and integrated team.

The traditional trilogy in the oncology arsenal, surgery, radiation, and chemotherapy, remains the essence of the current mainstream multimodal protocol using a combination of some or all. The best outcomes will be realized when the multimodal therapy is planned and coordinated. The surgeon talks to and collaborates with the radiation oncologist while involving the medical oncologist from the outset as well. This also includes empowerment and involvement of the pet's owners and family. These protocols are costly and time-consuming, and they require tweaking and adjustment throughout the course of treatment. A healthy client–doctor relationship is born from careful consultation with all specialists and the owner. All specialists must know the animal's status and special situation as well knowing the owner. This way nothing is "lost in translation" and confidence is maintained, resulting in a strong sense of trust.

Over the years, a volume of experiences has amassed and provided the wisdom to make these firm recommendations: plan, cooperate, and communicate. The surgeon, who operates on an animal with a solid tumor, then refers to a radiation oncologist to "mop up" residual disease has likely done the animal a disservice. Upfront surgical and radiation therapy planning minimizes surgical morbidity and minimizes normal tissue radiation injury while maximizing the efficacy of the union of modalities.

In the following sections the technology of multimodal therapy is presented in some detail using specific tumor settings to illustrate them. Underscoring this technology is the philosophy of this introduction and it cannot be overstated: the effective management of cancer in patients is a team event.

Surgery remains the mainstay for treating many types of cancer in pets, and the value of a competent surgical oncologist cannot be understated. The type of surgical mind-set, specific knowledge, and technical prowess required is a specialized skill. Such a surgeon appreciates and can deliver what is required to expertly attempt a surgical cure or completely change tack for a palliative or diagnostic approach and employ other modalities synergistically.

Radiation therapy as an addition to the available treatment options allows a greater scope and choice of therapy in many instances. Examples of tumors commonly treated with radiation include certain oral tumors, nasal tumors, brain tumors, mast cell tumors, and soft tissue sarcomas. Radiation can be used with palliative (e.g., to palliate bone pain with primary appendicular osteosarcoma) or curative intent and be used on its own or with surgery. For example, radiation can be used with surgery to treat a solid tumor in a location where wide clean margins cannot be achieved without limb amputation to save the limb. In this scenario, the radiation oncologist should be involved prior to surgery so that he or she can see if this approach is feasible; appreciate the size, fixation, and exact location of mass; plan the radiation field size and shape; determine how to spare normal tissue and include a large enough field; meet the owners; discuss complications, costs, expected outcome;

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etc. The surgeon's role in this setting is a delicate, minimal surgery with intent to preserve blood and oxygen supply to the tissue to increase the effectiveness of radiation. A marginal resection to remove all the macroscopic tumor and allow primary closure is performed, and radiation therapy is used with surgery to provide long-term tumor control or cure. This approach differs greatly from a failed curative-intent surgery and a poorly healed or open, hypoxic, radiation-resistant wound and a delayed start to radiation therapy: a situation that is avoided by a team approach and good planning.

When adjuvant radiation is planned, the surgeon can help the radiation oncologist by decreasing wound complications such as infection, dehiscence, and seroma formation. Preservation of blood supply, gentle tissue handling, aseptic technique, attention to hemostasis, use of fine, nonirritating (inert) suture material in minimal amounts, obliteration of dead space in the wound, avoidance of tension, postoperative rest, and use of bandages are all important. Drains should be avoided if possible, and if they are used, drainage entry and exit holes are included in the radiation field. Hemoclips can be placed in the wound intraoperatively to delineate the boundaries of the excised gross tumor burden to assist the radiation oncologist in planning the radiation field.

Radiation can be used postoperatively (as in the above scenario) or preoperatively or intraoperatively, depending on tumor type and location.

Sources of radiation therapy include megavoltage (>1 million electron volts of photon energy = high energy; maximum dose to tumor rather than skin) and orthovoltage (150–500 kVp = low energy; maximum dose to skin surface) external beam radiation, brachytherapy (interstitial placement of radioactive isotopes), or systemic or cavitary injection of radioisotopes (e.g., iodine-131). Megavoltage irradiation has advanced with 3D imaging and planning, multileaf collimators, custom-made blocks, etc.

Chemotherapy can sometimes be used neoadjuvantly to "down-stage" (shrink) a primary tumor prior to surgery, and thus make it more amenable to surgical resection with clean margins. This may be appropriate for cutaneous and subcutaneous masses such as mast cell tumors and hemangiosarcomas. In this setting the surgeon needs to involve the medical oncologist prior to surgery. Chemotherapy also can prolong life postoperatively by addressing systemic metastasis; the classic example is appendicular osteosarcoma in dogs. Chemotherapy can be used immediately postoperatively or once the wound has healed, at the discretion of the medical oncologist and the surgeon. Surgery may have only a small role, such as for diagnostic biopsy, with the sole treatment being chemotherapy, as is the case with lymphoma.

Metronomic chemotherapy uses standard chemotherapy agents in a continuous administration, which requires lower doses to be used. The target of the drug is the tumor's continually proliferating microvasculature, which is susceptible to chemotherapeutic effects with minimal systemic toxicity (Gately and Kerbel 2001).

Bisphosphonates concentrate within areas of active bone remodeling and induce osteoclast apoptosis, which is of therapeutic benefit in managing pathological bone resorptive conditions such as osteosarcoma, multiple myeloma, and metastatic bone cancer. Bone pain is decreased, quality of life is improved, and progression of bone lesions is delayed (Fan et al. 2007).

Other therapies that can be combined with more traditional therapies such as surgery, radiation, and chemotherapy include gene therapy, immunotherapy, and photodynamic therapy (PDT).

Molecular and targeted therapies show great potential. These therapies include gene therapy (e.g., viral and nonviral vectors); targeting signal transduction that regulates cell growth, differentiation, survival, and death (e.g., via inhibition of protein kinase); RNA (ribonucleic acid) interference (the use of double-stranded RNA to cause posttranscriptional gene silencing); antiangiogenic factors (including metronomic chemotherapy and cyclo-oxygenase-2 inhibitors); and telomerase (enzyme that maintains telomeres or the protective structures at ends of chromosomes). Ninety-five percent of all canine cancers are associated with telomerase activity, whereas almost all normal cells have no telomerase activity (Argyle et al. 2007).

Embolization treatments include "bland arterial embolization" (without chemotherapy) and chemoembolization (embolization with chemotherapeutic agents) that can be used as sole therapy or preoperatively to decrease tumor mass and size. Chemoembolization delivers chemotherapy to the tumor, allowing prolonged contact of the tumor to the chemotherapy without high systemic toxicity (Granov et al. 2005) and augmenting tumor ischemia (Weisse et al. 2002). There are several experimental studies of embolization treatments in healthy dogs, including chemoembolization with gemcitabine (Granov et al. 2005), carboplatin (Chen et al. 2004), and cisplatin (Nishioko et al. 1992). Bland arterial embolization resulted in decreased tumor growth, pain palliation, and control of hemorrhage in two dogs and one goat (Weisse et al. 2002) and decreased primary tumor size in a dog with a soft tissue sarcoma (Sun et al. 2002).

A thinking surgical oncologist is always aware of the animal as a whole and how the behavior of the

specific cancer in the specific patient influences the surgeon's role. The surgeon is cognizant of paraneoplastic syndromes, appropriate imaging and staging prior to and during surgery, appropriate supportive and follow-up care, and how various modalities can be used synergistically to achieve maximal outcome with minimal morbidity. Tables 2.1, 2.2, and 2.3 outline various treatment modalities and published outcomes of these treatments for various types of cancers in dogs and cats.

Table 2.1. Epithelial.

Neoplasia	Researched Treatment Options and Outcomes
Cutaneous Squamous Cell Carcinoma	Modalities include surgery, radiation therapy, surgery combined with radiation therapy, photodynamic therapy, imiquimod, intralesional chemotherapy (alone or combined with hyperthermia or radiation), vitamin A–related synthetic retinoids. Cryosurgery is used for small lesions, and there are partial responses with piroxicam in dogs.
Intranasal Carcinoma	For curative-intent radiation therapy (RT), median survival time (MST) is approximately 8–20 months. Curative-intent RT followed by surgical debulk (13 dogs) has MST of 47 months (Adams et al. 1987; Adams et al. 1998; Adams et al. 2005; Lana et al. 2004; McEntee et al. 1991; Nadeau et al. 2004; Theon et al. 1993). Curative–intent RT with CT planning has MST of approximately 11–20 months. Coarse-fraction RT (56 dogs) has MST of 7 months (Mellanby et al. 2002). Palliative 3D conformal RT (38 dogs) has overall median progression-free interval of 10 months (Buchholz et al. 2009). Chemotherapy alone (small numbers of dogs) is investigational (Hahn, Knapp, et al. 1992; Langova et al. 2004). Radiation sensitizers (some investigational) is generally not better than RT alone. Other treatments include brachytherapy, immunotherapy, cryotherapy, and PDT (all investigational) (Lucroy, Long, et al. 2003; MacEwen et al. 1977; Thompson et al. 1992; White et al. 1990; Withrow 1982).
Transitional Cell Carcinoma (urogenital)	Transitional cell carcinoma (TCC) (dogs): Bladder/urethra: Surgery includes debulk, stent, bypass (e.g., prepubic cystostomy catheter for palliation if obstructed). Rarely is there complete excision. Nephrectomy is performed if one ureter is obstructed; if both ureters are obstructed, there is no benefit to surgery. Debulking surgery alone for bladder TCC has MST of 109 days (Lengerich et al 1992). One dog treated with resection of proximal urethra and bladder neck and bilateral ureteroneocystostomy and adjuvant chemotherapy for bladder survived 580 days (Saulnier-Troff et al. 2008). Radiation: Complications of urinary incontinence and cystitis occurs with whole-bladder intraoperative radiation (Walker and Breider 1987; Withrow et al. 1989). Coarse fractionation external beam radiation (with mitoxantrone-piroxicam) showed no benefit over mitoxantrone-piroxicam chemotherapy alone (Poirier, Forrest et al. 2004). Laparoscopically implanted tissue-expander radiotherapy shows promise in reducing radiation damage to surrounding tissues (one dog still alive at 21 months) (Murphy et al. 2008). Medical: Mitoxantrone-piroxicam combination with minimal toxicity has a MST of 291 days (Henry et al. 2003). For piroxicam alone, palliative MST is 195 days (20% alive after 1 year) (Mutsaers et al. 2002). Concurrent antibiotics are commonly needed. PDT: PDT is currently under investigation (Lucroy, Ridgway et al. 2003; Ridgway and Lucroy 2003). Prostatic carcinoma: Prostatectomy is performed for early stage disease confined to prostate capsule (but there is a high rate of urinary incontinence) (Basinger et al. 1989; Hardie et al. 1984). Other treatment modalities include transurethral-resection (TUR) (electrosurgical and investigational; relieves urethral obstruction, but 2 of 3 dogs had perforated urethra) (Liptak, Brutscher et al. 2004); Nd:YAG laser (investigational: 8 dogs had MST of 103 days; 3 died from complications within 16 days) (L'Eplattenier et al. 2006); stenting (investigational but very promising, with good to excellent outcome in 8 dogs) (Weisse et al. 2006); bypass obstruction (prepubic catheter); chemotherapy (investigational); NSAIDs (MST 6.9 months in 16 dogs, compared to 0.7 months with no cancer therapy in 15 dogs) (Sorenmo, Goldschmidt, et al. 2004); intraoperative prostatic radiation (MST for 10 dogs was 114 days) (Turrel 1987a); PDT (investigational) (Lucroy, Bowles et al. 2003; L'Eplattenier et al. 2008); and palliative radiation for skeletal metastasis.

(*Continued*)

Table 2.1. (*Continued*)

Neoplasia	Researched Treatment Options and Outcomes
Solitary Primary Lung Mass	Surgery (lung lobectomy) is performed. All adjuvant chemotherapy is investigational at this stage: systemic chemotherapy (vinorelbine) (Poirier, Burgess et al. 2004); inhalational chemotherapy (Hershey et al. 1999; Vail et al. 2000); intrapleural chemotherapy for malignant pleural effusion (Moore, Kirk et al. 1991).
Thymoma	Resection is done if possible (about 70%), along with chemotherapy (Aronsohn 1985; Atwater et al. 1994; Willard et al. 1980; Martin et al. 1986, especially if concurrent with megaesophagus relating to a poor surgical candidates); radiation therapy has complete to partial responses, and many also received concurrent surgery or chemotherapy (Hitt et al. 1987; Kaser-Hotz et al. 2001; Smith et al. 2001). Treatment of concurrent myasthenia gravis is accomplished with immunosuppressive and or anticholinesterase therapy, H2 blockers, other supportive care.
Intestinal	Intestinal: Modalities include surgery with wide margins (at least 5 cm); adjuvant doxorubicin chemotherapy in cats with colonic adenocarcinoma (Slaweinski et al. 1997); intracavitary chemotherapy for carcinomatosis (Moore, Kirk et al. 1991); adjuvant doxorubicin chemotherapy in dogs (Paoloni et al. 2002); piroxicam palliative for rectal tubulopapillary polyps if unresectable or as alternative to surgery (Knottenbelt et al. 2000).
Anal Sac Adenocarcinoma (see Figure 2.1)	Surgery for primary tumor and regional (sublumbar) lymph nodes (repeated surgical removal of metastatic lesions may afford prolonged survival) (Hobson et al. 2006); debulking and omentalization of sublumbar nodes when nonresectable (Hoelzler et al. 2001); adjuvant radiation for local tumor and nodal metastasis; systemic chemotherapy (various protocols) (Goldschmidt and Zoltowski 1981; Williams et al. 2003; Turek et al. 2003; Ross et al. 1991; Bennett et al. 2002).
Mammary	Surgery is the treatment of choice, except for inflammatory carcinoma or if distant metastasis is present. Surgery includes nodulectomy, mammectomy, regional mastectomy, unilateral or bilateral mastectomy, and also lymph node removal for staging. The surgical choice depends on benign versus malignant, size, number, and species (cat versus dog). In cats, adequate surgical treatment combined with adjuvant chemotherapy may be of benefit to prolong survival time over surgery alone. In one paper, the MST of cats that received surgery and doxorubicin was 448 days, and the median disease-free interval (DFI) was 255 days (Novosad et al. 2006). There is no known proven effective adjuvant chemotherapy protocol for malignant or metastatic mammary tumors in dogs. Some preliminary studies show promise; in 14 dogs with stage III disease (T3 N0 M0) and 2 dogs with stage IV disease (any T N1 M0), half had cyclophosphamide and 5-FU, and half had regional mastectomy alone. The dogs receiving adjuvant chemotherapy had improved survival and disease-free interval (Karayannopoulou et al. 2001). Another study showed adjuvant gemcitabine chemotherapy postsurgery in dogs had no benefit (Marconato et al 2008). Doxorubicin and cyclophosphamide or cisplatin has some antitumor effect against mammary adenocarcinoma. Doxorubicin is associated with partial response with duration of 12 and 16 months in 2 dogs with metastatic mammary adenocarcinoma (Hahn, Richardson et al. 1992). Doxorubicin increases membrane viscosity and lipid hydroxyperoxide, and this effect is increased with concurrent medroxyprogesterone acetate (Pagnini et al. 2000). Doxorubicin has better efficacy than platinum drugs, and carboplatin and cisplatin have the same efficacy in mammary tumor cell culture; efficacy is not affected by cell type (adenocarcinoma, solid, mixed cell) (Simon et al. 2001). Piroxicam plus radiation therapy has produced best results with inflammatory carcinoma. In 44 human patients with inflammatory breast carcinoma, an 81% response rate was achieved with combination therapy (fluorouracil, doxorubicin, cyclophosphamide, mastectomy, and adjuvant paclitaxel) (Cristofanilli et al. 2001). Adjuvant chemotherapy is investigational, considered if poor prognostic factors are present (e.g., large, lymph node–positive, invasive, high grade), and administered after complete surgical removal (Lana et al. 2007).

Table 2.1. (*Continued*)

Neoplasia	Researched Treatment Options and Outcomes
	Immunomodulation appears ineffective to date (Lana et al. 2007). Ovariohysterectomy early in life is preventative. Ovariohysterectomy as part of treatment is still not proven clearly to be of benefit (Fowler et al. 1974; Brodey et al. 1983; Morris et al. 1998; Yamagami et al. 1996; Sorenmo, Shofer et al. 2000). Tamoxifen is not recommended (Morris et al. 1993).
Salivary Gland Carcinoma	Surgery is used for aggressive removal where possible, along with adjuvant radiation if there is incomplete resection (Carberry et al. 1987; Hammer et al. 2001; Evans and Thrall 1983; Carberry et al. 1988), and chemotherapy (investigational).
Ear Carcinoma	Surgery is used (conservative if benign, radical if malignant, resectable, and no metastases) (Marino et al. 1994; Marino et al. 1993; London et al. 1996). Radiation is used as an alternative to surgery if unresectable or as adjuvant to incomplete resection (Theon et al. 1994); PDT used for local disease.
Ovarian Carcinoma	Ovariohysterectomy: Intracavitary cisplatin for malignant effusion (Moore, Kirk et al. 1991; Olsen et al. 1994). Platinum drugs with tamoxifen used in metastatic human ovarian tumors. Hectate-b significantly reduces tumor burden (Gawronska et al. 2002). Chemotherapy has potential to prolong life in animals with metastatic ovarian cancer.
Uterine Carcinoma	Uterine adenocarcinoma in cats: Treatment is ovariohysterectomy. Role and effectiveness of radiation and chemotherapy is unknown.
Insulinoma	Modalities include surgery (resection primary, staging, debulking metastases), frequent feeds, prednisolone, streptozotocin, diazoxide, and octreotide (Feldman and Nelson 2004; Leifer et al. 1986; Tobin et al. 1999; Robben et al. 1997; Moore et al. 2002).
Thyroid Carcinoma	Dogs: Mobile thyroidectomy (Carver et al. 1995; Klein et al. 1995; Panciera et al. 2004), fixed/nonresectable radiation therapy treatment of choice 80% for 1-year survival, 72% for 3-year survival (Theon et al. 2000). ^{131}I thyroid ablation can give prolonged survival in dogs with nonresectable thyroid carcinoma, with local/regional tumor MST at 839 days and MST 366 days for metastasis (Adams et al. 1995; Panciera et al. 2004; Peterson et al. 1989; Turrel et al. 2006; Worth et al. 2005). Chemotherapy is considered as adjuvant treatment for nonresectable primary or large primary carcinoma (>27 cm^3), bilateral disease, or for gross metastatic disease) (Theon et al. 2000; Jeglum and Whereat 1983; Fineman et al. 1998; Post and Mauldin 1992; Ogilvie et al. 1991; Hammer et al. 1994; Gallick et al. 1993; Leav et al. 1976). Boron neutron capture therapy is investigational (Pisarev et al. 2006).
Hyperthyroid Cats	Multinodular adenomatous hyperplasia (70%–75%), solitary benign adenomas (20%–25%), malignant carcinomas (1%–3%) (Bailey and Page 2007). ^{131}I thyroid ablation is treatment of choice: oral antithyroid medication, topical methimasole to pinna, thyroidectomy (Padgett 2002; Flanders 1999), ultrasound-guided percutaneous ethanol injections (Wells et al. 2001), ultrasound-guided percutaneous radiofrequency ablation (Mellary et al. 2003). Preoperative scintigraphy is ideal (Bailey and Page 2007).

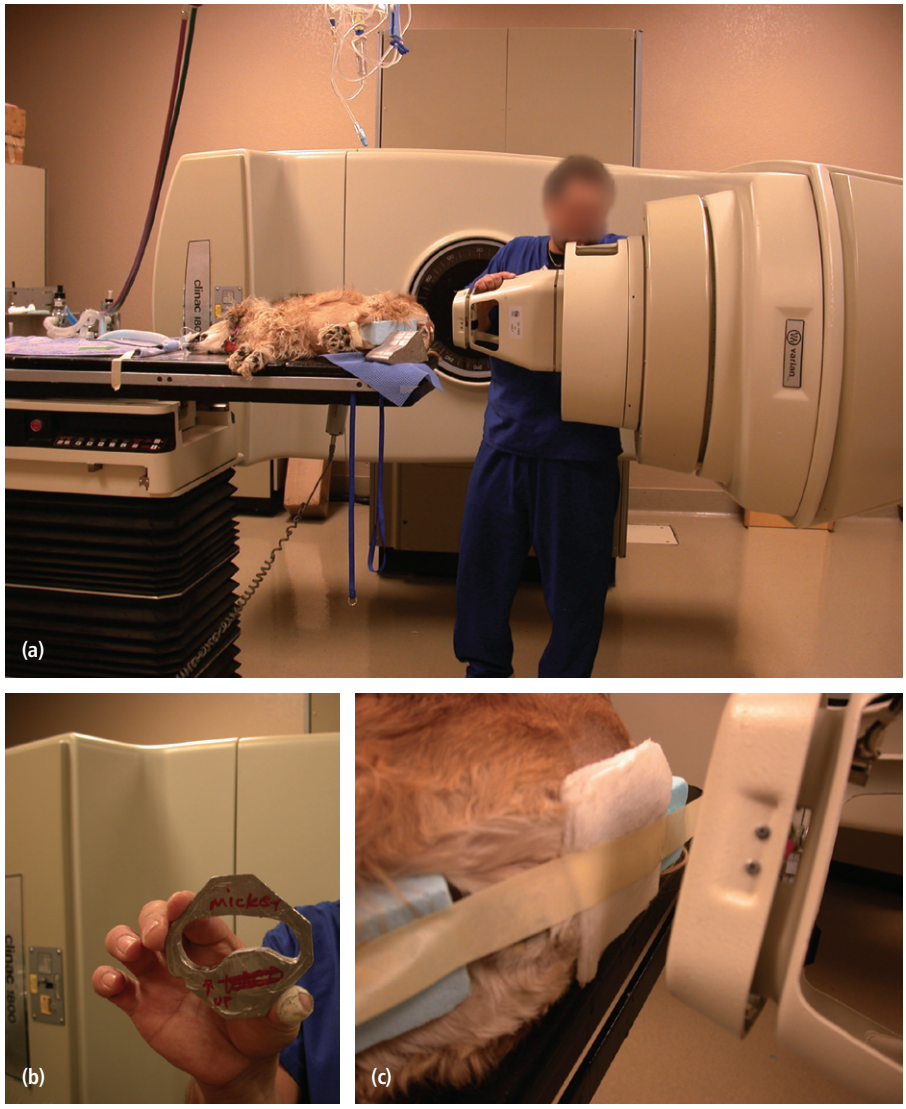

Figure 2.1. (A) Anal sac adenocarcinomas treated with adjuvant megavoltage radiation. (B) Lead block used to spare normal tissue from RT. (C) Final setup including a tissue–equivalent "bolus" to allow the maximum dose of radiation to reach the tumor. (Courtesy of Mary-Kay Klein)

Table 2.2. Round cell.

Neoplasia	Researched Treatment Options and Outcomes
Mast Cell Tumor	Marginal surgery with adjuvant radiation results in 85%–95% 2-year control for stage 0, grade I or II (Turrel et al. 1988; Al-Sarraf et al. 1996; Frimberger et al. 1997; LaDue et al. 1998). Other modalities include marginal surgery with adjuvant chemotherapy (vinblastine and prednisolone; see Figure 2.2) (Davies et al. 2004), surgery with curative intent (2–3 cm margins depending on grade) (Simpson et al. 2004), vinblastine-prednisolone chemotherapy as adjuvant to surgery for high risk (mucous membrane origin, node positive, high-grade) (Thamm et al. 2006). Chemotherapy may also be used for dogs with multiple cutaneous mast cell tumors. The need for adjuvant chemotherapy for completely excised grade II tumors (when not in a poor prognostic location) is unpredictable; close monitoring is advisable (Seguin et al. 2001). A recent paper suggested dogs with a mitotic index (MI; number of mitoses per 10 high-power fields) is prognostic, with animals with MI = 0 not reaching median survival, animals with MI between 1 and 7 with MST of 18 months, and dogs with MI > 7 with a MST of 3 months (Elston et al. 2009). A higher MI may help identify which subset of grade II mast cell tumors would benefit from adjuvant chemotherapy. Other chemotherapy agents include lomustine, vincristine, prednisolone/cyclophosphamide/vinblastine, cyclophosphamide/vincristine/prednisolone/hydroxyurea (Elmslie 1997; McCaw et al. 1997; Rassnick et al. 1999; Davies et al. 2004; Thamm et al. 1999; Gerritsen et al. 1988), vinorelbine (Grant et al. 2008), inhibitors of tyrosine kinase (SU11654), both direct antitumor and antiangiogenic activity (London et al. 2003; Liao et al. 2002). Other adjunctive medical therapies include H1 blocker, H2 blocker, omeprazole, sucralfate, and misoprostol. Pretreatment with prednisone prior to surgery (neoadjuvant) can reduce the size of mast cell tumors, facilitating resection with adequate margins in situations where margins cannot be confidently attained because of mass location or size or both (Stanclift and Gilson 2008).
Plasma Cell Tumor	Multiple myeloma treatment modalities include chemotherapy using melphalan and prednisolone standard, as well as cyclophosphamide, CCNU, chlorambucil, doxorubicin, vincristine (Matus et al. 1986; MacEwen and Hurvitz 1977; Hanna 2005; Drazner 1982; Brunnert et al. 1992; Osborne et al. 1968; Gentilini et al. 2005; Fan et al. 2002; Vail 2007); surgery (stabilization of pathological fractures; see Figure 2.3) (Vail 2007; Banks et al. 2003) with or without adjuvant radiation therapy, bisphosphonates (Vail 2007); tyrosine kinase–inhibitor therapy SU11654 (London et al. 2003). Extramedullary treatment modalities (cutaneous) include conservative surgical resection (can add chemotherapy if local recurrence or incomplete margins) (Rusbridge et al. 1999; Kryiazidou et al. 1989). Radiation alone for stable solitary osseous plasmacytoma (MacEwen et al. 1984; Rusbridge et al. 1999; Meis et al. 1987). Surgery plus radiation for solitary osseous plasmacytoma resulting in an unstable long-bone fracture or surgery with or without radiation for solitary osseous plasmacytoma resulting in neurological compromise (Vail 2007).
Lymphoma	Various chemotherapy protocols (Boyce and Kitchell 2000; Carter et al. 1987; Cotter and Goldstein 1983; Garrett et al. 2002; Greenlee et al. 1990; Khanna et al. 1998; Keller et al. 1993; MacEwen et al. 1981; MacEwen et al. 1987; Morrison-Collister et al. 2003; Mutsaers et al. 2002; Myers et al. 1997; Page et al. 1992; Postorino et al. 1989; Stone et al. 1991; Valerius et al. 1997; Zenman et al. 1998) immunotherapy (investigational) (MacEwen et al. 1985; Crow et al. 1977; Jeglum et al. 1988; Steplewski et al. 1990; Rosales et al. 1988; Jeglum 1996); radiation therapy for whole body (localize stage I or stage II disease for nasal or CNS lymphoma, palliation of local disease) (Vail and Young 2007); bone marrow transplantation and staged half-body radiation after remission with induction of chemotherapy—both investigational (Williams et al. 2004; Gustavson et al. 2004)—or surgery for solitary lymphoma (early stage I) or solitary extranodal, or splenectomy for massive splenomegaly due to lymphosarcoma (Moldovanu et al. 1966; Brooks et al. 1987) or surgery for obstructive or ruptured gastrointestinal lymphoma (Marks 2001).

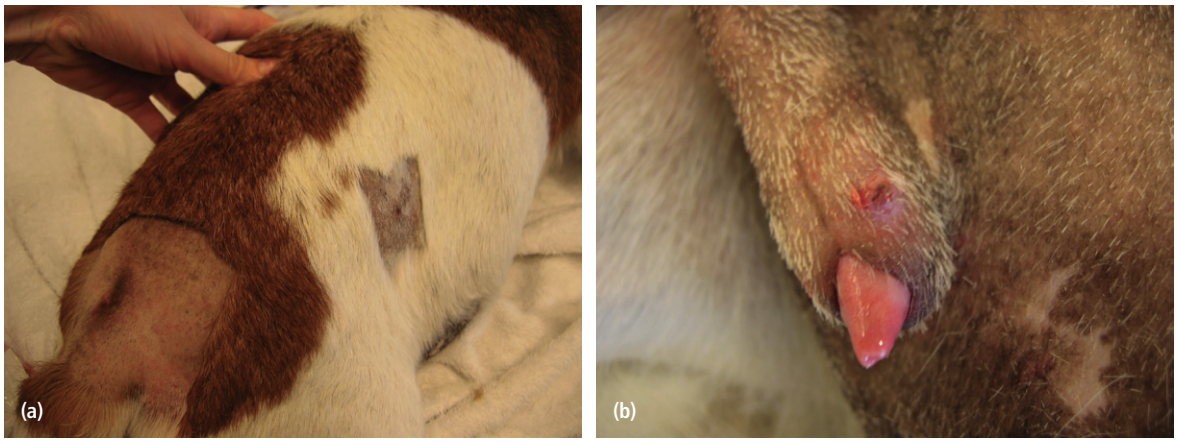

Figure 2.2. (A) Terrier breed dog with concurrent multiple mast cell tumors and previous history of having had several other mast cell tumors removed. (B) Same dog as (A), with tumor in a poor prognostic location (prepuce). This dog was treated with multiple marginal resections and adjuvant chemotherapy.

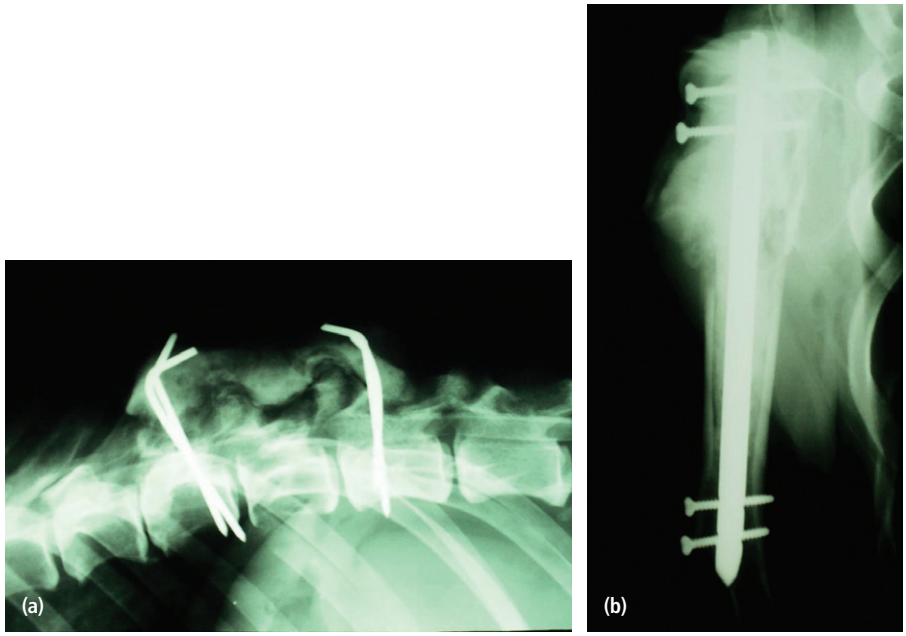

Figure 2.3. (A) Multiple myeloma causing a pathological fracture of T12, treated with surgical stabilization and adjuvant chemotherapy. (B) Same dog as in (A), with surgical stabilization of a subsequent pathological fracture of the humerus. This dog survived approximately 8 months due to a combination of surgery and chemotherapy.

Table 2.3. Mesenchymal.

Neoplasia	Researched Treatment Options and Outcomes
Soft Tissue Sarcoma (Schwannoma, neurofibroma, peripheral nerve sheath tumor, etc.)	Surgery, wide margins, with curative intent (Baez et al. 2004; Banks, Straw et al. 2003; Banks, Straw et al. 2004; Dernell, Withrow et al. 1998; Kuntz et al. 1997; Posterino et al. 1988), surgery-marginal resection with adjuvant radiation (Evans 1987; Forrest et al. 2000; Graves et al. 1988; McKnight et al. 2000); systemic chemotherapy of possible benefit for highly anaplastic tumors but as yet unproven for grade III soft tissue carcinomas (Selting et al. 2000). Marginal resection and localized cisplatin chemotherapy into wound bed (OPLA-Pt/Atrigel) as yet still investigational (Banks and Straw 2003). Metronomic chemotherapy (continuous low-dose chemotherapy) with cyclophosphamide and piroxicam significantly increased disease-free interval for incompletely resected soft tissue sarcomas compared to control dogs (Elmslie et al. 2008).
Vaccine-Associated Sarcomas in Cats	Surgery (Davidson et al. 1997; Hershey et al. 2000; Kuntz CA unpublished data; Lidbetter et al. 2002; McEntee and Page 2001); surgery and radiation therapy (Cohen et al. 2001; Cronin et al. 1998; Bregazzi et al. 2001; Kobayashi et al. 2002), chemotherapy (Barber et al. 2000; Poirier et al. 2004; Bregazzi et al. 2001); immunotherapy (Jourdier et al. 2003; Kent 1993; King et al. 1995; Quintin-Colonna et al. 1996).
Intermuscular Lipoma	Careful surgical dissection (peeling out), excellent prognosis (Thomson et al. 1999).
Infiltrative Lipoma	Aggressive surgical resection, adjuvant radiation if margins incomplete (McEntee and Thrall 2001).
Liposarcoma	Wide surgical resection with clean margins yields good prognosis (Baez et al. 2004). Adjuvant radiation if incomplete resection.
Mesothelioma	Surgery, usually debulking, pericardiectomy for palliation (surgical or thoracoscopic), intracavitary and/or intravenous chemotherapy (Closa et al. 1999; Dunning et al. 1998; Jackson et al. 1999; Kerstetter et al. 1997; Moore, Kirk et al. 1991; Stepien et al. 2000; Seo et al. 2007; Sparkes et al. 2005; Spugnini et al. 2008). Early metastasis a concern even if complete resection achieved (Liptak and Brebner 2006).
Lymphangiosarcoma	Surgery, chemotherapy, radiation therapy (all investigational, as very little reported) (Itoh et al. 2004).
Synovial Cell Sarcoma	Surgery (high amputation is treatment of choice because local recurrence is higher with marginal or wide resection) (Vail et al. 1994); chemotherapy may be of benefit if sarcoma is high grade and there is no metastasis, or if the node is positive (Vail et al. 1994; Tilmant et al. 1986). Adjuvant radiation for incomplete excision investigational.
Oral Fibrosarcoma	Surgical resection with wide margins is treatment of choice (Lascelles et al. 2003; Schwarz et al. 1991a; Schwarz et al. 1991b; White 1991); if not resectable with clean margins, surgery and radiation therapy (unreported) or radiation therapy alone (palliative) (Thrall 1981). Systemic chemotherapy has no known benefit. For histologically low-grade, biologically high-grade oral fibrosarcoma, prognosis depends upon early diagnosis and aggressive treatment. Prolonged survival can be achieved in some dogs with surgery, radiotherapy alone, surgery and radiotherapy, and radiotherapy and local hyperthermia (Ciekot et al. 1994).
Oral Melanoma	For local disease, surgery with wide clean margins (Kudnig et al. 2003; Ramos-Vara et al. 2000; Kosovsky et al. 1991; Wallace et al. 1992; Schwarz et al. 1991a; Schwarz et al 1991b; Overly et al. 2001; MacEwen et al. 1986; Harvey et al. 1981; Hahn et al. 1994); repeat surgery with wide margins or adjuvant radiation therapy if margins incomplete; radiation therapy alone (Freeman et al. 2003; Bateman et al. 1994; Blackwood and Dobson 1996; Theon et al. 1997; Turrel 1987b; Proulx et al. 2003; Farrelly et al. 2004). Regional lymph node metastasis treatment includes surgery and or radiation therapy; chemotherapy (partial responses) (Kudnig et al. 2003; Overly et al. 2001; Rassnick et al. 2001; Page et al. 1991); immunotherapy (investigational) (Alexander et al. 2006; Bergman, Camps-Palau et al. 2003; Bergman, MacEwen et al. 2003; Bergman et al. 2004; Dow et al. 1998; Elmslie et al. 1994; Elmslie et al. 1995; MacEwen et al. 1999; Moore et al. 1991; Quintin-Colonna et al. 1996).

(*Continued*)

Table 2.3. (*Continued*)

Neoplasia	Researched Treatment Options and Outcomes
Cutaneous Melanoma	Surgical excision is treatment of choice (Bolon et al. 1990; Aronsohn and Carpenter 1990); chemotherapy shows little response (Ogilvie et al. 1991; Moore 1993; Gillick and Spiegle 1987; Rassnick et al. 2001); hyperthermia and intralesional cisplatin/carboplatin (Theon et al. 1991) and PDT (Cheli et al. 1987; Dougherty et al. 1981) have short-lived responses. Radiation therapy likely to be of use if melanoma not surgically excisable (Vail and Withrow 2007). Immunomodulation is investigational (Hogge et al. 1999; Dow et al. 1998; Hajduch et al. 1997; Quintin-Colonna et al. 1996; Alexander et al. 2006; MacEwen et al. 1999; Bergman et al. 2006; Bianco et al. 2003; Gyorffy et al. 2005).
Appendicular Osteosarcoma	Surgery (amputation/limb-spare) (Vasseur 1987; Berg et al. 1992; LaRue et al. 1989; Thrall et al. 1990; Withrow et al. 1993; Morello et al. 2003; Buracco et al. 2002; Ehrhart 2005; Tomamassini et al. 2000; Ehrhart et al. 2002; Rovesti et al. 2002; Seguin et al. 2003; Pooya et al. 2004; Liptak, Dernell, et al. 2004; Huber et al. 2000); hemipelvectomy (Straw et al. 1992); partial scapulectomy (Trout et al. 1995; Kirpensteijn et al. 1994); ulnectomy (Straw et al. 1991). Local chemotherapy as adjuvant to limb-sparing (OPLA-Pt) reduced local recurrence rate (Straw et al. 1994; Withrow et al. 2004). Local chemotherapy (isolated limb perfusion) (Van Ginkel et al. 1995) as adjuvant to limb-sparing (investigational); radiation therapy to primary site (palliative as alternative to amputation/limb-spare) (McEntee et al. 1993; Ramirez et al. 1999; Mueller et al. 2005; Green et al. 2002; Heidner et al. 1991); adjunctive to limb-spare (Thrall et al. 1990; Withrow et al. 1993), radioisotopes (Milner et al. 1998; Aas et al. 1999); chemotherapy (various protocols) adjuvant to limb-spare or amputation (clear benefit) (Thompson and Fugent 1992; Bergman et al. 1996; Berg et al. 1995; Berg et al. 1997; Kent et al. 2004); chemotherapy neoadjuvant to limb-sparing to downstage disease presurgery (Withrow et al. 1993; O'Brien et al. 1996); chemotherapy as an adjuvant to palliative radiation (role unclear) (Walter et al. 2005).
Multilobular Osteochondrosarcoma	Surgery as cure of local disease, prolonged survival if local disease cured (MST 14 months even if metastasis present at diagnosis) (Dernell, Straw et al. 1998). If surgical removal not possible, consider surgical debulk plus adjuvant radiation therapy (Straw et al. 1989).
Chondrosarcoma	Wide surgical excision significantly improves survival. Median survival time is 540 days treated with amputation alone (Popovitch et al. 1994); chest wall resection MST 1,080 days (Pirkey-Ehrhart et al. 1995); wide surgical excision for nonnasal sites MST of 3,097 days and did not reach MST (Waltman et al. 2007); and MST 979 days for 25 dogs with appendicular chondrosarcoma treated with amputation alone, although grade was found to be prognostic (Farese et al. 2009). Debulking and adjuvant radiation therapy if location is not amenable to curative resection, to radiation alone (Popovitch et al. 1994; Lana et al. 1997), or have objective responses to coarse fraction radiation alone (Dernell 2007). Metastasis still occurs in about 25%, even after surgical resection. Grade may be prognostic for survival (Waltman et al. 2007; Farese et al. 2009).
Cutaneous Hemangiosarcomas (HSA)	Dogs: Stage I surgery (MST 780 days), stage II and III surgery (and adjuvant doxorubicin chemotherapy should be considered) (Ward et al. 1994). Twenty-one dogs with subcutaneous (17) and intramuscular (4) hemangiosarcomas, with adequate local tumor control and no metastasis at presentation, were treated with adjuvant doxorubicin. Five dogs also received adjuvant radiation therapy. The MST for subcutaneous HSA was 1,189 days and for intramuscular was 272.5 days (Bulakowski et al 2008). Cats: Wide surgical excision (metastasis occurs less frequently than dogs, but adjuvant chemotherapy may have a role, depending on the case) (Miller et al. 1992; Kraje et al. 1999; McAbee et al. 2005). Radiation therapy is considered adjuvantly if incompletely resected local disease.

Table 2.3. (*Continued*)

Neoplasia	Researched Treatment Options and Outcomes
Visceral HSA	Surgery (e.g., splenectomy) (Spangler and Culbertson 1992; Spangler and Kass 1997; Brown et al. 1985; Sorenmo, Baez, et al. 2004; Prymak et al. 1988); adjuvant chemotherapy of various types can be considered for splenic hemangiosarcomas, with median survival times of 141–179 days reported (Ogilvie et al. 1996; Hammer et al. 1991; Sorenmo, Duda, et al. 2000; Sorenmo, Baez et al. 2004; Sorenmo, Samluk, et al. 2004; Sorenmo et al. 1993; Vail et al. 1995). Immunotherapy (Vail et al. 1995) and angiogenic therapy are investigational (Sorenmo, Duda, et al. 2000).
Histiocytic Sarcomas	Localized (skin/subcutis): Aggressive surgery with clean margins (Affolter and Moore 2002); adjuvant radiation therapy if incomplete resection; adjuvant chemotherapy (unknown role but likely to be warranted due to high metastatic potential) (Liptak and Forrest 2007). Disseminated/malignant histiocytosis: Chemotherapy can give durable partial responses but is generally unrewarding (Skorupski et al. 2003).
Uterine Leiomyoma and Leiomyosarcoma in Dogs	Prognosis good with complete surgical resection.
Vaginal and Vulval Tumors	Most are benign (leiomyoma and fibroma in cat, leiomyoma and lipoma in dog).

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3

Interventional oncology

William T.N. Culp

Interventional radiology (IR) is a specialty that uses different imaging modalities to direct minimally invasive diagnostic and therapeutic procedures. IR has become a well-established and integral speciality in human medicine and is rapidly growing in veterinary medicine. The influx of IR techniques in veterinary medicine allows veterinary clinicians the ability to offer patients advanced treatment options that were previously unavailable. Interventional oncology (IO) is a subspecialty of IR that is focused on the treatment of oncologic disease.

When performing IO procedures, it is essential for the veterinary clinician to have a firm grasp of different imaging modalities and basic surgical procedures, as surgically approaching blood vessels is often necessary. IO procedures such as vascular stenting, intraarterial chemotherapy, and transarterial embolization/chemoembolization are performed intravascularly, and specialized sheaths, guidewires, and catheters are needed for these interventions. Nonvascular diseases such as malignant obstructions and effusions can also be treated with IO techniques and involve the placement of stents and long-term catheters.

Many of the current applications of IO in veterinary patients are palliative; in these cases, the primary goal is to improve quality of life while causing minimal morbidity. IO can also provide treatment options in cases that were previously considered untreatable. Reports on the use of IO in veterinary patients are limited, but investigation of IO applications in human medicine offers insight into the vast benefits that this expanding specialty can offer for our veterinary patients. A systematic discussion of the imaging, instrumentation, and techniques involved in IO will be discussed below.

Imaging

A complete knowledge of the vascular anatomy is mandatory for performing vascular interventions. Additionally, the interventional radiologist should have a thorough understanding of the imaging modalities and contrast agents that are used to perform IO procedures. While imaging modalities such as fluoroscopy, computed tomography, and magnetic resonance imaging are commonly employed by veterinary clinicians, the use of these modalities for IO treatments is largely unreported, aside from isolated case reports and small case series.

Modalities

Stenting procedures can be performed solely with digital radiography, although fluoroscopy is superior as it allows for real-time evaluation of the anatomy. Fluoroscopy is mandatory when performing IO procedures that require vascular interventions. A fluoroscopy unit (C-arm) with specifications including digital subtraction, road-mapping ability, collimation, and low patient radiation dosing are ideal. Ceiling mounting should be pursued when possible, and the C-arm should have the ability to acquire complex oblique views. Newer units allow the interventional radiologist to perform image acquisition and most other C-arm operations at the bedside, eliminating the need for an assistant to perform these tasks in a control room.

While angiography performed with fluoroscopic guidance allows for excellent evaluation of the direction and velocity of blood flow, the images obtained are in two-dimensional planes and only display the lumen of the vessel (Green and Parker 2003). Computed tomographic angiography (CTA) and magnetic resonance

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angiography (MRA) are rapidly developing imaging modalities that have certain advantages over fluoroscopy, including noninvasive angiographic image acquisition, less patient postprocedure discomfort, and volumetric and cross-sectional image analysis (Green and Parker 2003; Hellinger and Rubin 2006; Thornton and Grist 2006). The volumetric and cross-sectional image analysis that is obtained with CTA and MRA allows vessels to be evaluated in multiple directions with a single scan, whereas several images and injections of contrast are necessary to gain the same information using fluoroscopy (Hellinger and Rubin 2006). Advances are being made that allow CTA and MRA to be performed simultaneously with interventional techniques, which may result in more efficient and accurate IO procedures in the future (Ladd et al. 2000; Hellinger and Rubin 2006; Thornton and Grist 2006; Kos et al. 2008).

Ultrasound has many applications in IR. Many of the disease processes that may require IO treatments can be diagnosed by ultrasonography. In dogs, hepatocellular carcinoma, a tumor commonly treated by chemoembolization and radiofrequency ablation in humans (Okusaka et al. 2009; Hiraoka et al. 2010), is easily identified by abdominal ultrasound (Liptak, Dernell et al. 2004). In one study of dogs with hepatocellular carcinoma, diagnosis of a hepatic mass was made with ultrasound in 93.5% of cases (Liptak, Dernell et al. 2004). Other tumors that may require an IO treatment, such as urethral, colonic, and thyroid neoplasia, can also be evaluated by ultrasound (Hume et al. 2006; Weisse et al. 2006; Barber 2007). In a recent case series of dogs with masses obstructing hepatic venous outflow, masses were often identified by ultrasonography (Schlisksup et al. 2009). In addition to the diagnostic utility of ultrasound, this modality is regularly employed in humans to aid in obtaining vascular access (to initiate the Seldinger technique) during performance of IR procedures (Longo et al. 1994; Dodd et al. 1996; Ahmad et al. 2008; Arthurs et al. 2008). Ultrasound can also be used to perform procedures, including the placement of drainage catheters, percutaneous biopsies, percutaneous ethanol injection of hepatic neoplasia, and radiofrequency ablation (Longo et al. 1994; Dodd et al. 1996; Solbiati 1998).

Contrast agents

Contrast agents are required components of most intravascular procedures and many stenting procedures. The predominant contrast agents used for angiography include iodinated agents, gadolinium-based agents, and carbon dioxide (Ehrmann et al. 1994; Moresco et al. 2000; Spinosa et al. 2000; Spinosa et al. 2001; Brown et al. 2003; Namasivayam et al. 2006; Bui et al. 2007). Iodinated contrast agents are available in both ionic and nonionic forms; nonionic agents are less osmolar than their ionic counterparts (Singh and Daftary 2008). Severe reactions are reported to occur with similar incidence among all iodinated contrast agents, but mild and moderate contrast reactions occur more commonly with the use of higher osmolality iodinated contrast agents (Singh and Daftary 2008). Nephrotoxicity is a major potential complication associated with the use of iodinated contrast agents and has become the third most common cause of acute renal failure in humans (Akgun et al. 2006). The most commonly used iodinated contrast agents are the nonionic monomers such as iohexol, iopromide, iopamidol, and ioversol (Dickinson and Kam 2008).

Gadolinium-based contrast agents and CO_2 are used most commonly in patients who have had a previous adverse reaction to an iodinated contrast agent and in those patients with an increased risk for development of nephrotoxicity (Moresco et al. 2000; Spinosa et al. 2000; Spinosa et al. 2001; Dickinson and Kam 2008), although some recent studies have reported nephrotoxicity in association with gadolinium contrast usage (Akgun et al. 2006; Ergün et al. 2006). Agents such as gadopentetate dimeglumine, gadodiamide, gadoteridol, and gadoversetamide are the most readily available gadolinium-based contrast agents (Akgun et al. 2006) and are used when previous CO_2 usage has resulted in a suboptimal study due to bowel gas artifacts or as a supplement to CO_2 angiography (Spinosa et al. 2000; Spinosa et al. 2001). Gadolinium-based contrast agents produce less detailed contrast studies as compared with iodinated agents and are therefore less useful for angiography during IR procedures (Spinosa et al. 2000). When using gadolinium-based contrast agents, digital subtraction angiography is recommended to compensate for the less detailed study that is otherwise obtained (Spinosa et al. 2000).

To outline a hollow viscus such as the esophagus, urethra, and colon, substances such as barium and iodinated contrast agents have been used (Hume et al. 2006; Weisse et al. 2006; Farese et al. 2008). In a recent study of esophageal tumors in dogs, barium sulfate was found to be useful in identifying mass location (Farese et al. 2008). In dogs, iodinated contrast agents have been used to evaluate urethral obstructions prior to urethral stenting (Weisse et al. 2006). Additionally, an iodinated contrast agent was used prior to colonic stenting to delineate colonic obstructions secondary to adenocarcinoma in cats (Hume et al. 2006).

Instrumentation and Implants

Access needles

Traditional hypodermic needles or over-the-needle catheters (Figure 3.1) can be used to puncture vessels

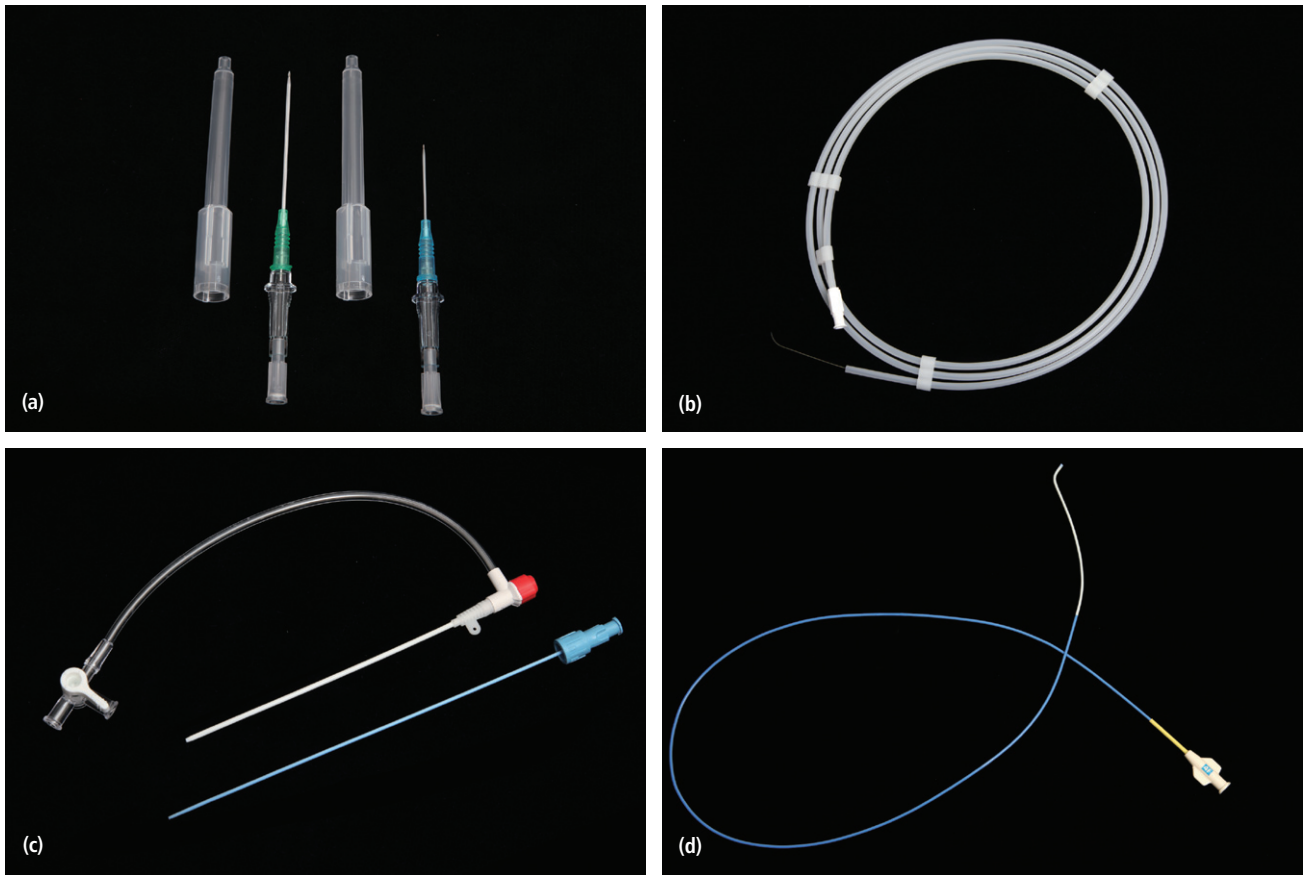

Figure 3.1. Interventional oncology instrumentation. From left to right: (A) 18-gauge over-the-needle catheter (left), 22-gauge over-the-needle catheter (right). (B) 0.035-inch hydrophilic guidewire. (C) Dilator and vascular access sheath. (D) Catheter with angled-tip.

when obtaining vascular access using the Seldinger technique (Seldinger 1953). The size of the access needle used determines the wire size that can be introduced through the needle and into the vessel. The standard venous access needle is an 18-gauge needle, which accepts guidewires up to 0.38 inches in diameter (Braun 1997). A 21-gauge needle is considered to be a micropuncture needle and allows for introduction of guidewires up to 0.018 inches in diameter (Braun 1997; Valji 2006).

Guidewires

Selection of a particular guidewire (Figure 3.1) is dictated by the size of access needle that has been placed, the technique to be performed, and the vessel(s) to be selected. Most guidewires are available in three standard lengths: 150 cm, 180 cm, and 260 cm (Braun 1997). Alternative lengths of 60 cm, 125 cm, and 145 cm have been reported, but these are not readily available (Valji 2006; Kipling et al. 2009). The standard diameters of most guidewires are 0.035 and 0.038 inches. Smaller gauge wires of 0.014 and 0.018 inches are used when microcatheters and smaller (micropuncture) vascular access needles are used (Braun 1997; Valji 2006; Kipling et al. 2009).

There are a few primary principles that must be adhered to when using guidewires. First, most guidewires contain a hydrophilic coating made of polytetrafluoroethylene that needs to be primed with saline to allow for smooth passage through the lumen that has been selected (Braun 1997; Kipling et al. 2009). When sufficiently wet, the guidewire should pass easily through a catheter and allow an increased ability to perform vascular selection (Braun 1997; Kipling et al. 2009). It is essential that the guidewire remain wet during the procedure to improve guidewire function (Kipling et al. 2009). Second, the length of the selected guidewire should be at least twice the length of the catheter that is being used (Braun 1997). Third, if a guidewire is not passing easily through a vascular access needle, the needle may need to be repositioned. The wire should not be forced as the needle may be subintimal or against a sidewall (Valji 2006). Lastly, a torque device can be placed on the end of a guidewire (approximately 5–10 cm from a catheter hub that has been introduced over the guidewire) to better manipulate and steer the

guidewire (Kipling et al. 2009). These torque devices can be invaluable when passing a guidewire into vessels that are difficult to access and when crossing stenotic regions.

Guidewires are also used for nonvascular stenting procedures (Hume et al. 2006; Weisse et al. 2006; Culp et al. 2007; Kipling et al. 2009). Stents that are placed through malignant obstructions are introduced over a guidewire, and the stent delivery system tapers down to the guidewire to allow for easier placement. In companion animals, 0.035-inch hydrophilic guidewires have been used to facilitate stent placement for tracheal, urethral, and colonic obstructions (Hume et al. 2006; Weisse et al. 2006; Culp et al. 2007).

Sheaths

The use of intravascular sheaths (Figure 3.1) is indicated when a procedure involves multiple exchanges into and out of a vessel. The sheath protects the vessel wall from damage and allows for easier passage of different catheter types. Additionally, sheaths protect the vessel from stiff intravascular devices, balloon catheters, and intravascular foreign bodies (Braun 1997; Valji 2006; Stavropoulos et al. 2006).

A dilator that tapers down to a guidewire is usually present within a sheath and allows expansion of the previously made hole in the blood vessel. Sheaths contain a valve that prevents blood leakage while allowing entrance of specialized catheters, wires, stents, snares, and biopsy forceps (Snow and O'Connell 2000; Stavropoulos et al. 2006). Additionally, sheaths contain a sidearm that allows for injection of contrast, which can pass around wires and nonocclusive catheters (Snow and O'Connell 2000; Valji 2006). The French gauge of a sheath is determined by the largest gauge catheter that can fit through the sheath and represents the inner diameter of the sheath (Braun 1997; Snow and O'Connell 2000). The French size of a sheath is generally considered to be 2 French gauges smaller than the outer diameter (Valji 2006).

In human medicine, sheaths have also been used for nonvascular procedures such as antegrade ureteric stenting, percutaneous transhepatic biliary drainage, and colonic stenting (Braun 1997; Snow and O'Connell 2000). The use of sheaths in urethral stenting has been described in veterinary medicine (Weisse et al. 2006; Newman et al. 2009). Some sheaths are designed with a peel-away component that is used during the placement of venous access devices and drainage catheters (Braun 1997). The peel-away component allows a device to be inserted through the sheath, and the sheath can then be removed while leaving the device in place.

Catheters

When performing intravascular procedures, there are many catheter types that are available to the interventional radiologist. Decisions about which catheter is most optimal for a specific procedure is based on experience and the anatomy of the vessel that is to be selected. In human medicine, catheters with an outer diameter of 5 French (1 French = 3 mm) (Silberstein et al. 1992; Valji 2006) are chosen most commonly. (Braun 1997). This catheter size has the advantage of having good torque control and high flow rates when contrast is injected (Braun 1997). A larger catheter (6–7 French) affords the user increased control of torque (Wojtowycz 1990a; Braun 1997). Commonly used catheters are made of nylon, Teflon, or polyurethane (Wojtowycz 1990a; Valji 2006).

Catheters are often categorized by the shape of the tip, with the basic catheter tip shapes being straight, pigtail, hook and angled (Braun 1997; Valji 2006). Straight catheters are commonly used for embolotherapy (delivery of a vascular occlusion agent) and for opacification of a vascular tree; however, care should be taken when injecting through a straight catheter with a single end-on hole as injury to the vessel is possible (Braun 1997). Pigtail catheters are superior for opacification, as they allow for the injection of a bolus of contrast through several small holes in the catheter, thus preventing the jet effect that may be seen with straight catheters (Wojtowycz 1990a; Braun 1997; Valji 2006). Pigtail catheters should be removed over a guidewire so that the catheter is straight during removal and therefore less likely to cause vascular damage (Wojtowycz 1990a). Hook catheters, such as the shepherd's hook and cobra catheters, are used to catheterize vessels that have acute angled branches (Braun 1997). These visceral catheters are advanced over a guidewire to the desired location. The catheters are then allowed to reform (take on the original shape of the catheter) in a large vessel (generally aorta or vena cava) and are then gently pulled back into the lumen of the vessel selected (Braun 1997). Angled-tip catheters (Figure 3.1) are used in the selection of upward-branching vessels; as with other catheters, a guidewire is often used to facilitate vessel selection and to maintain position once it has been established (Braun 1997). The Berenstein catheter is an example of an angled-tip catheter (Braun 1997).

Similar to sheaths and guidewires, catheters can be used for nonvascular techniques. When stenting luminal obstructions, such as in the urethra or trachea, marker catheters are employed to determine appropriate stent size (Hume et al. 2006; Weisse et al. 2006; Culp et al. 2007; Newman et al. 2009). Another nonvascular

oncologic use includes palliation of malignant thoracic and abdominal effusions by placing catheters for percutaneous drainage. This has been described in several human studies (Brooks and Herzog 2006; Fleming et al. 2009). Pigtail catheters are often used for draining malignant effusions since they have multiple fenestrations; a locking loop mechanism that maintains the catheter position in the desired location is also present on some pigtail catheters.

When performing IO techniques, there are certain techniques and principles of catheter usage that are important to understand, namely the coaxial technique, the so-called rule of 110, and superselective catheterization with guidewire-microcatheter combination. As the size of a vessel that is being targeted for catheterization decreases, the catheter diameter must also decrease. Placement of a catheter that is too large can result in damage to the vessel wall, blood stasis with subsequent tissue ischemia, difficulty in removing the catheter, and vessel rupture (Stavropoulos et al. 2006). The coaxial technique is commonly employed to introduce progressively smaller catheters and wires to allow for superselection of vessels while minimizing the risk for development of complications. Simply stated, this technique involves placement of a smaller wire or catheter (depending on the stage of the procedure) into a catheter that is already within the blood vessel. The smaller wires and catheters share the same axis as the indwelling catheter, thus the term *coaxial* is used. This technique has been described in human patients undergoing selection of small vessels (Korogi et al. 1995; Tajima et al. 2008).

A guide for vessel selection (particularly celiac and superior mesenteric arteries in humans) has been described and termed the "rule of 110" (Chuang 1981; Nemcek 1996). According to Chuang (1981), this rule states that "both the length and width of the catheter tip should be about 110% of the width of the aorta at the level of the artery (that is to be selected) as it branches". The width refers to the distance between the tip of the catheter and the proximal straight limb of the catheter (Chuang 1981). If this technique is employed with a catheter of appropriate size and tip, the tip of the catheter should engage the branching vessel (i.e., celiac, cranial mesenteric, or renal artery in dogs and cats) as the catheter is pulled caudally and should subsequently enter the chosen vessel.

A guidewire can be combined with a microcatheter (using the coaxial technique) to allow for superselective catheterization. To accomplish this, the guidewire-microcatheter combination is passed through a guiding catheter to a vessel branch that is a few orders less than the desired branch (Stavropoulos et al. 2006). The guidewire-microcatheter combination is then advanced toward the desired branch, and the guidewire is used to select the desired branch. The catheter is then immediately but gently advanced over the guidewire and into the vessel to prevent the guidewire from backing out. This should be performed in a series of steps that are slow and calculated (Stavropoulos et al. 2006). The guidewire can then be advanced further into the vessel or into a smaller branching vessel as needed.

Vascular closure devices

A vascular closure device is an instrument used to close the hole in a blood vessel that remains after removal of a vascular access sheath. The use of arteriotomy closure devices is well documented in human interventional cardiologic medicine; however, the use of these devices in veterinary medicine is uncommon (Meyerson et al. 2002; Koreny et al. 2004; Nikolsky et al. 2004). Historically, manual compression combined with bed rest was used to control bleeding at an arteriotomy site (Hoffer and Bloch et al. 2003). Concerns over the high rates of bleeding at these high-pressure sites spurred the development and use of devices that can be used to close vessels after a vascular IO procedure has been performed (Dauerman et al. 2007). Benefits seen with the use of closure devices have included decreased time to hemostasis and earlier ambulation (Meyerson et al. 2002; Tron et al. 2002; Hoffer and Bloch 2003; Dauerman et al. 2007). Closure devices are not universally used in human cases, however, and some studies have suggested similar or higher complication rates associated with the use of closure devices as compared to manual compression (Meyerson et al. 2002; Nikolsky et al. 2004; Dauerman et al. 2007).

Vascular closure devices can be divided into two categories: passive and active (Silber 1998; Meyerson et al. 2002; Tron et al. 2002; Dauerman et al. 2007). Passive closure devices assist or enhance manual compression and do not provide immediate (<5 min) hemostasis (Dauerman et al. 2007). Examples of passive closure devices (devices enhancing manual compression) include patches, wire-stimulated track thrombosis, and pneumatic pressure devices (Nader et al. 2002; Applegate et al. 2007; Dauerman et al. 2007; Doyle et al. 2007; Jensen et al. 2008). Over the last decade, active closure devices have been used more commonly as compared to passive closure devices (Dauerman et al. 2007). Active closure devices include collagen-based devices that may or may not have an anchor or suture included, suture alone devices, and staple/clip devices (Dauerman et al. 2007). Further development of active closure devices is being pursued, and it remains to be seen if these devices gain universal acceptance among those performing arteriotomy for IR procedures.

Vascular occlusion agents and devices

To perform vascular occlusion via IO methods, a thorough understanding of the occlusive agents is mandatory. Two broad categories, based on the positioning of the agents in the vessels exists: those delivered into the vessel and carried passively to a target vessel (particles and liquids) and those that are positioned at the site where occlusion is needed (coils and balloons) (Kunstlinger et al. 1981; Ginat et al. 2009, Loffroy et al. 2009). The agent chosen depends on the goal of the procedure; multiple agents may be indicated and used in the same patient.

Particles

Collagen sponges, conventional polyvinyl alcohol (PVA), and microspheres are the most commonly used particles (Loffroy et al. 2009). Collagen sponge particles are used for temporary occlusion (Abada and Golzarian 2007). Most studies suggest that recanalization occurs within 14 days (Abada and Golzarian 2007; Loffroy et al. 2009); however, one study found that 78% of cases were recanalized at 3 days (Louail et al. 2006). These sponges likely perform occlusion through physical effects and by enhancing thrombus formation (Abada and Golzarian 2007; Loffroy et al. 2009).

Conventional or nonspherical PVA particles are available in multiple sizes. These particles cause mechanical occlusion, and the subsequent blood stasis results in biological occlusion (Loffroy et al. 2009). Nonspherical PVA particles have an irregular shape and may aggregate, resulting in a more proximal occlusion; for instance, a third-order vessel branch may be occluded when a fourth-order branch occlusion is desired (Siskin et al. 2000; Loffroy et al. 2009). Nonspherical PVA particles are considered permanent vascular occlusion agents (Siskin et al. 2000; Patel and Soulen 2006); however, some reports have described recanalization of vessels that have been occluded with these particles (Siskin et al. 2000; Loffroy et al. 2009).

The majority of microspheres that are commercially available are made of trisacryl gelatin, PVA, or sodium acrylate/vinyl alcohol copolymer (Patel and Soulen 2006; Loffroy et al. 2009). Microspheres are available in 100–300 μm, 300–500 μm, 500–700 μm, 700–900 μm, and 900–1,200 μm (Laurent 2007). Microspheres have several advantages over nonspherical PVA particles. Microspheres can be calibrated (developed with a predetermined size), and tend to reduce blood flow more quickly and reliably than nonspherical PVA (Laurent 2007; Loffroy et al. 2009). Nonspherical PVA particles can have variable behavior after discharge from a catheter, making the placement of these particles less predictable than microspheres (Laurent 2007). Another advantage of microspheres as compared to nonspherical PVA is that they do not result in catheter blockage as they do not aggregate prematurely (Loffroy et al. 2009).

Improvements in microsphere technology have allowed for even more sophisticated IO techniques. Microspheres with drug-eluting capabilities are available and allow for delivery of high-dose chemotherapy directly to a tumor, with minimal systemic effects (Liapi et al. 2007; Martin et al. 2009). Some of the drugs that have been incorporated into microspheres include doxorubicin, oxaliplatin, and irinotecan (Liapi et al. 2007; Kettenbach et al. 2008; Martin et al. 2009).

Further advancements in microsphere production include the use of microspheres that can be detected on MRIs and CTs and microspheres that can be resorbed in a controlled manner (Laurent 2007). Being able to visualize the location of a microsphere with CT and MRI allows the clinician to determine the final location of the microspheres and the subsequent tumor response based on that location. Resorption of the microsphere may allow these particles to be used for temporary occlusion.

Liquids

Several liquid agents are available for use in vascular occlusion including biological glues (such as cyanoacrylate), sclerosing agents, and gelling solutions (Loffroy et al. 2009). Liquids are not commonly used in the vascular occlusion of tumors. Cyanoacrylate embolizes very quickly upon contact with blood and endothelium (Greenfield 1980; Loewe et al. 2002; Patel and Soulen 2006). In cases of hepatocellular carcinoma that have been deemed nonresectable, glue has been used as an embolic agent (Loewe et al. 2002; Rand et al. 2005). Additionally, humans with liver or biliary neoplasia are sometimes treated by glue embolization of a portal vein branch preoperatively; this induces hypertrophy of the remaining liver (Nagino et al. 1995; deBaere et al. 2010). This hypertrophy of normal tissue may prevent liver failure after resection of the primary tumor (Nagino et al. 1995; deBaere et al. 2010). Sclerosing agents such as ethanol are used for embolotherapy. These agents cause necrosis of the blood vessel wall, and the resulting protein denaturation that occurs results in thrombus formation. Disadvantages of ethanol usage are the associated toxicities such as skin lesions, peripheral nerve palsy, renal failure, thrombophlebitis, lack of radiopacity and postoperative pain (Wojtowycz 1990b; Valji 2006; Loffroy et al. 2009). In humans, ethanol has been successfully used in several reports for the embolization of renal neoplasia (Wojtowycz 1990b; Munro et al. 2003; Schwartz et al. 2006; Maxwell et al. 2007; Ginat et al. 2009). Gelling

solutions consist of a polymer in a solvent, and the commercially available form is PVA copolymer in dimethylsulphoxide (Loffroy et al. 2009). These solutions have been used for treating arteriovenous malformations and endoleaks (persistent aneurysmal sac perfusion after endovascular repair); however, further investigation is necessary to elucidate the role of these agents in the treatment of neoplastic disease (Ginat et al. 2009; Lv et al. 2009; Stiefel et al. 2009; Nevala et al. 2010).

Coils

Coils are the most commonly used mechanical embolization device. Most coils are constructed from stainless steel, platinum, or nitinol; threads are often attached to increase thrombogenic potential (Lustberg and Pollak 2006; Valji 2006; Ginat et al. 2009). Coils can be made in a variety of shapes and sizes and are often delivered from a 5 French angiography catheter or 3 French microcatheter (Wojtowycz 1990b; Lustberg and Pollak 2006). A coil should be properly sized to the vessel that is being embolized. A coil that is too large may not fully "coil," and as a result protrude into a feeding vessel (Wojtowycz 1990b). A coil that is too small can migrate distally or proximally, leading to embolization of the wrong vessel (Valji 2006). Coils are generally used in the embolization of nononcologic disease such as arteriovenous fistulas and traumatic bleeds; however, reports of coils for the preoperative embolization or definitive treatment of renal, biliary, and hepatic neoplasia exist (Madoff et al. 2003; Munro et al. 2003; Schwartz et al. 2006; Maxwell et al. 2007). Indications for renal embolization may include preoperative infarction, treatment of metastatic renal neoplasia, nonresectable renal neoplasia, and patients who elect not to undergo radical excision (Munro et al. 2003; Schwartz et al. 2006; Maxwell et al. 2007).

Balloons

Balloons can be used for vascular occlusion in both a temporary (nondetachable) and a permanent (detachable) fashion. Temporary occlusion or partial occlusion with a nondetachable balloon may be beneficial when delivering particulate embolic agents (Greenfield et al. 1978). The balloon can be used to decrease the rate of blood flow to prevent unwanted occlusion at a distal site (Greenfield et al. 1978). The use of detachable balloons as a permanent vascular occlusion device has fallen out of favor as newer permanent vascular occlusion agents have developed (Lustberg and Pollak 2006).

Stents

Vascular and nonvascular stents have revolutionized the treatment of many human diseases. While stents are commonly used in human medicine to treat coronary artery disease, stents are also used to treat benign and malignant obstructions (Pron et al. 1999; Jamshidi et al. 2008; Lewis 2008; Phillips et al. 2008; Foo et al. 2010). Technological improvements in stents are constantly being made, and stents specific to veterinary needs have been created.

Both self-expanding and balloon-expandable stents are available, and the choice of stent is dependent on the intended purpose and location of deployment. Self-expanding stents have the advantages of being more flexible and easier to navigate through angled or tortuous vessels as compared with balloon-expandable stents (Valji 2006). Additionally, self-expanding stents should be used in vessels with variable diameters, as these stents will conform to the changing diameter along that vessel (Valji 2006). Balloon-expandable stents tend to have greater radial force and hoop strength as compared to self-expanding stents, but also may experience collapse after placement (Valji 2006).

Stents are most commonly composed of stainless steel or metal alloys such as nitinol (nickel-titanium) and elgiloy (cobalt-chromium) and may have a covering of polyurethane, polyethylene terephthalate, polytetrafluoroethylene, or silicone (Stoeckel et al. 2002; Valji 2006; Jamshidi et al. 2008; Lewis 2008; Hanawa 2009). Ureteral stents are composed of polyethylene, polyurethane, hydrogel, silicone, or thermoplastic polymer and are formed into a tube; metal ureteral stents have also been used (Auge and Preminger 2002; Liatsikos et al. 2009; Venkatesan et al. 2010).

Several different methods are used to fabricate stents. The majority of stents are made from laser cutting (Stoeckel et al. 2002). Other fabrication techniques include photochemical etching, waterjet cutting, braiding, knitting, and coiling (Stoeckel et al. 2002). The method used to make each stent should be reviewed by the interventional radiologist as this affects the deployment and eventual configuration of the stent. For instance, braided designs will shorten after expansion, and it is critical to understand this if the appropriate size stent is to be selected (Stoeckel et al. 2002).

Vascular obstructions may require stent placement to restore the vascular lumen. Budd-Chiari syndrome is manifested by hepatic venous outflow obstruction secondary to a myriad of diseases, including malignant neoplasia (Beckett and Olliff 2008). The primary nonvascular regions where stent placement can be beneficial include the biliary tree, esophagus, colon, urethra, ureter, trachea/bronchus, and lacrimal duct (Pron et al. 1999). Malignant obstructions are the primary indications for placement of stents in these locations (Pron et al. 1999).

Recent advances in stent technology have included development of drug-eluting stents, removable stents, radioactive stents, and absorbable stents. Drug-eluting stents are used commonly in human medicine, and drugs such as paclitaxel have been embedded into the coating on the stent (Ong and Serruys 2005; Lewis 2008). Drug-eluting stents are most commonly used for cardiovascular disease in humans (Lewis 2008), although clinical cases of hepatobiliary malignancy have been treated with drug-eluting stents (Suk et al. 2007). Additionally, paclitaxel-eluting stents have been evaluated in the urinary tracts of pigs and dogs (Shin et al. 2005; Liatsikos et al. 2007). Removable and absorbable stents are being used in human IR (Lootz et al. 2001; Tammela and Talja 2003; Grabow et al. 2005; Lewis 2008; McLoughlin and Byrne 2008; Kotsar et al. 2010); however, the application for removable and absorbable stents in veterinary IO is likely to be limited. Further research is needed to evaluate the use of radioactive stents, but early research and clinical results are hopeful (Liu et al. 2007; Liu, Lu et al. 2009). These stents provide an intraluminal source of brachytherapy with the goal of local tumor control (Balter 1998; Liu et al. 2007; Liu, Lu et al. 2009).

Approaches

Vascular

The majority of veterinary IO vascular procedures are performed through three major vessels: the carotid artery, femoral artery, and jugular vein. For all approaches, the hair over the surgical site is clipped, and the site is prepared with aseptic technique and draped. The approach to the carotid artery and jugular vein are made with the animal in dorsal recumbency; the neck is outstretched and the head is maintained parallel to the tabletop. For a femoral artery approach, the patient is also placed in dorsal recumbency and the femoral pulse is palpated. The hind limb will often need to be pulled gently away from the body to allow for appropriate exposure of the inguinal region.

In human medicine, ultrasound guidance is often used to gain vascular access (Ahmad et al. 2008; Arthurs et al. 2008); in veterinary patients, this is less common but should be explored further. The surgical approach is similar for access to the arteries. A 1–2 cm skin incision is made directly over the vessel to be accessed; generally, the incision is parallel to the direction of the vessel. The subcutaneous tissue is bluntly and sharply dissected until the desired vessel is easily palpable or visible. The tissue surrounding the vessel is then gently dissected and the vessel is manipulated to allow circumferential freeing of the vessel. A length of at least 1 cm of vessel should be freed from the surrounding tissue. When approaching the femoral or carotid artery, the vessels may be ligated at the conclusion of the procedure (Perkins and Edmark 1971; Moss 1974; Clendenin and Conrad 1979a; Clendenin and Conrad 1979b). A stab incision into the skin can be used when approaching the jugular vein, and dissection around the jugular vein is generally not necessary. Given the lower pressures found in the jugular vein, ligation is not necessary, as gentle pressure applied at the conclusion of the procedure will often maintain hemostasis.

The original technique for gaining vascular access was described by Seldinger in 1953, and this technique remains the primary means for obtaining vascular access for IO procedures (Higgs et al. 2005). An over-the-needle intravascular (IV) catheter (18, 21, or 22 gauge) is used to puncture the vessel, and the catheter is then advanced into the vessel. When puncturing the vessel, the needle should be advanced into the vessel at a 45-degree angle (Valji 2006; Stavropoulos et al. 2006). When a sufficient flash of blood has been noted (in humans, this is considered a 4- to 6-inch spurt in a normotensive person), the needle is removed, and a guidewire is introduced into the IV catheter and subsequently into the vessel. The IV catheter is then removed by backing it out of the vessel over the guidewire. A vascular access sheath-dilator combination is placed over the guidewire and gentle pressure is applied to manipulate the vascular access sheath-dilator combination into the vessel. A slight twisting motion may be necessary to introduce the vascular access sheath-dilator combination into the vessel. The dilator is removed from the vascular access sheath over the guidewire.

With the guidewire and vascular access sheath in place, specific vessels can be selected. A catheter is often placed over the guidewire and through the vascular access sheath to perform a myriad of diagnostic and treatment techniques. Agents such as contrast and embolic materials can be injected through the catheter when the area of interest has been identified. Additionally, other catheters and guidewires can be used through the specialized catheter using the coaxial technique.

Natural orifices

A surgical approach to address malignant obstructions in the trachea, esophagus, colon, and urethra is generally not necessary when pursuing IO treatment options. Furthermore, ureteral stents can be placed cystoscopically, and biliary stents can be placed with endoscopic guidance. For the placement of most tracheal, esophageal, colonic, and urethral stents, the patient is positioned in

lateral recumbency on the fluoroscopy table. The fluoroscopy monitor and necessary equipment should be within reach of the interventional radiologist. Standard sets should include an appropriately sized stent, sterile saline, sterile bowls, guidewire, and marker catheter. For esophageal, colonic, and urethral stents, a straight or slightly angled-tip catheter and iodinated contrast material should be easily accessible. An access sheath is recommended for the placement of urethral stents and should be placed in the distal urethra (Weisse et al. 2006).

Nonvascular Interventional Oncology Techniques

Stents

Tracheobronchial neoplasia

Tracheobronchial stenosis secondary to neoplasia can result in severe and often life-threatening clinical signs in human and veterinary patients. When possible, resection of the stenotic region should be attempted (Shin et al. 2006; Withrow 2007). Neoplastic disease may be extensive, however, precluding the successful use of surgery. Intraluminal tracheobronchial stenting has developed as a treatment option in cases where surgery is not recommended or not elected by human patients (Lee 2000; Husain et al. 2007; Kim et al. 2009).

Intraluminal tracheal stenting has been well-described in veterinary medicine for the treatment of tracheal collapse (Moritz et al. 2004; Sura and Krahwinkel 2008). Currently, only one case of intraluminal tracheal stenting to treat tracheal neoplasia has been documented in the veterinary literature (Culp et al. 2007). In that cat, a 2.6 cm long tracheal carcinoma was diagnosed, and the owners elected to perform intraluminal tracheal stenting to palliate the clinical signs. The clinical signs were relieved for a period of 6 weeks until metastatic disease was noted in the pulmonary parenchyma and the owners elected euthanasia. No complications associated with the intraluminal tracheal stenting procedure or postprocedure were noted, although a necropsy was not performed (Culp et al. 2007).

Ureteral neoplasia

Ureteral and bladder neoplasia can extend over the ureteral papilla and can prevent urine flow from the kidney to the bladder. External compression from other abdominal neoplasia (prostatic, bladder, cervical, uterine, ovarian, colorectal) can also result in compression of the ureter (Kulkarni and Bellamy 2001; Auge and Preminger 2002; Liatsikos et al. 2009). Ureteral stent placement to relieve obstruction has resulted in excellent outcomes in human patients (Kulkarni and Bellamy 2001; Auge and Preminger 2002; Liatsikos et al. 2009). Follow-up times of 35 months have been reported in human patients, and ureteral patency was maintained during that time (Kulkarni and Bellamy 2001).

Ureteral neoplasia in dogs and cats is exceedingly rare. Reports of ureteral neoplasia in dogs are limited to case reports and have included spindle cell sarcoma, transitional cell carcinoma, and leiomyosarcoma (Berzon 1979; Hanika and Rebar 1980; Guilherme et al. 2007). Benign masses diagnosed in the canine ureter include fibropapilloma and fibroepithelial polyps (Hattel et al. 1986; Reichle et al. 2003; Farrell et al. 2006). Ureteral stenting was recently reported as a treatment option in the management of ureteral obstruction secondary to neoplasia, although outcome data is currently lacking (Berent et al. 2007).

Bladder, urethral, and prostatic neoplasia

In dogs, the trigone of the bladder is the region of the urinary tract most commonly affected by neoplasia; these tumors regularly spread into the urethra (Mutsaers et al. 2003; Saulnier-Troff et al. 2008). Most tumors of the bladder and urethra are malignant (97%), and transitional cell carcinoma accounts for 87% of all canine bladder and urethral tumors (Norris et al. 1992). Radical surgical resection of tumors in the trigonal region is generally not recommended as recurrence and incontinence are common and bladder necrosis has been reported (Stone et al. 1996; Saulnier-Troff et al. 2008). Electrosurgical, laser, and vaporization techniques have also been described and carry a concern for urethral rupture (Liptak, Brutscher et al. 2004). Median survival times for surgical resection alone have been reported as 86–125 days (Lengerich et al. 1992; Norris et al. 1992; Helfand et al. 1994).

Canine prostatic neoplasia carries a poor to grave prognosis due to effects of local disease and due to a high metastatic rate (Freitag et al. 2007). The most common tumors affecting the prostate are adenocarcinoma and undifferentiated carcinoma, and several treatment modalities, including surgery, radiotherapy, and chemotherapy, have been attempted with mixed success (Freitag et al. 2007). Metastatic rates as high as 89% have been reported (Weisse et al. 2006). Locally, prostatic neoplasia can result in urethral obstruction and subsequent urine retention (Weisse et al. 2006).

While surgical debulking/resection, chemotherapy, and radiotherapy can be options for initial treatment of nonobstructive bladder or urethral transitional cell carcinoma, these are not good options for immediate relief of complete urethral obstruction secondary to bladder or urethral transitional cell carcinoma. Similarly, prostatic resection and/or radiation may result in local tumor

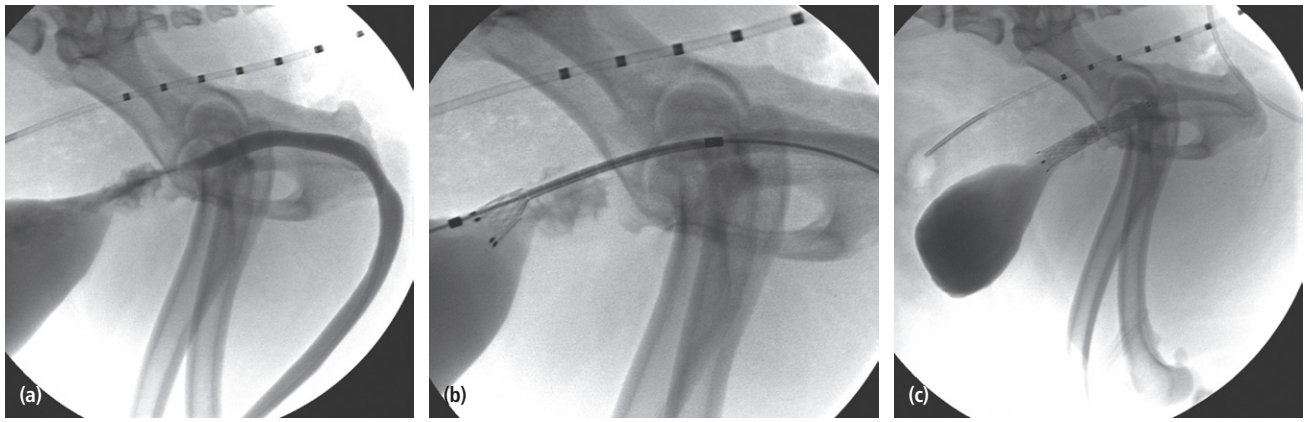

Figure 3.2. Urethral stent placement (neoplastic obstruction). (A) An area of obstruction can be noted cranial to the femoral head during this contrast study. A marker catheter is present within the rectum. (B) A stent within a delivery system can be seen in the urethra. The stent has been placed over a guidewire and is starting to be deployed. (C) Complete stent deployment has occurred, and the urethral obstruction is relieved.

control, but the high metastatic rate and risk of incontinence associated with surgical resection causes many owners not to pursue these options (Goldsmid and Bellenger 1991; Freitag et al. 2007). Palliation of urethral obstructions by the placement of urethral stents has been extensively described in human medicine (Sertcelik et al. 2000; DeVocht et al. 2003; Denys et al. 2004; Eisenberg et al. 2007; Seoane-Rodriguez et al. 2007; Woo et al. 2008), and experience is increasing in veterinary research (Ko et al. 2002; Yoon et al. 2006; Crisóstomo et al. 2007) and clinical medicine (Weisse et al. 2006; Newman et al. 2009). This technique is generally well tolerated and is one of the more simple and most commonly performed IO procedures in veterinary medicine (Figure 3.2).

The use of urethral stents to treat bladder, urethra, and prostatic neoplasia in a clinical setting has been evaluated in a single canine case series (Weisse et al. 2006) and in a single feline case report (Newman et al. 2009). In the canine cases, obstruction was relieved in all 12 dogs immediately after the procedure, and 11 of 12 dogs were urinating voluntarily. Incontinence and stranguria after stent placement was noted in several cases; however, 10 of 12 dogs were considered to have a fair to excellent outcome (Weisse et al. 2006). A balloon-expandable metallic stent was successfully used to relieve urethral obstruction in a cat diagnosed with urothelial carcinoma (Newman et al. 2009). Evaluation of long-term outcome was not possible as the cat developed progressive azotemia and was euthanized (Newman et al. 2009).

Colorectal neoplasia

The treatment of choice for nonlymphomatous colorectal tumors in dogs and cats is surgical excision. Several surgical procedures have been described, and extensive margins (from 2 to 8 cm) are recommended when considering the resection of a malignant neoplasm (Palmintieri 1966; White and Gorman 1987; Anson et al. 1988; Danova et al. 2006; Morello et al. 2008). In one study, dogs with annular, obstructing adenocarcinoma had mean survival times of 1.6 months versus 32 months in dogs with single, pedunculated colorectal adenocarcinoma (Church et al. 1987).

In humans with colorectal neoplasia, approximately 20% will present with unresectable locally advanced tumors or with metastatic disease, and between 10% and 30% will have acute colonic obstruction (Athreya et al. 2006; Wasserberg and Kaufman 2007). Colonic stenting is one of the palliative treatment options that can be offered in these cases (Suzuki et al. 2004; Athreya et al. 2006; Wasserberg and Kaufman 2007). Colonic stenting is also being used in human patients prior to surgical resection (Martinez-Santos et al. 2002; Suzuki et al. 2004). Patients with stents placed prior to definitive surgery may have lower severe complication rates and shorter hospital stays (Martinez-Santos et al. 2002).

Currently, only two cases of colonic stenting have been reported in veterinary clinical cases (Hume et al. 2006). In two cats with colonic adenocarcinoma, one survived for 274 days after stent placement and experienced minimal stent-associated side effects (occasional mild tenesmus) (Hume et al. 2006). The second was euthanized 19 days after stent placement due to a diminishing quality of life. Both cats retained fecal continence after stent placement (Hume et al. 2006). Colorectal stents may provide a viable treatment option in dogs as well (Figure 3.3).

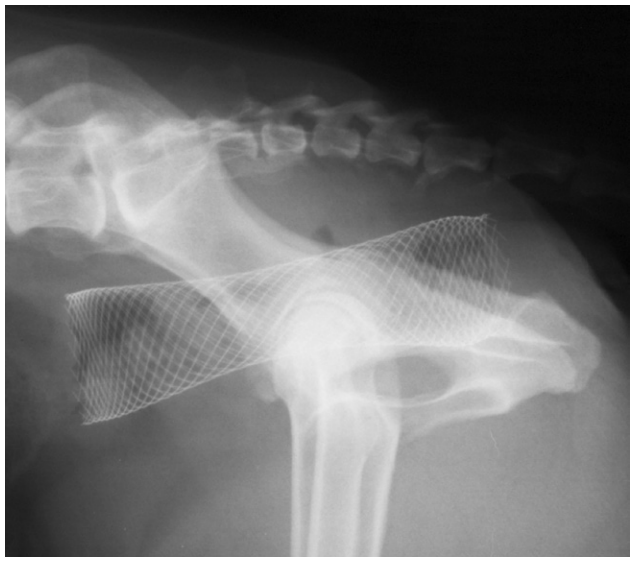

Figure 3.3. Colorectal stent (neoplastic obstruction). In this dog, a stent was placed to palliate clinical signs associated with a large annular colorectal neoplasm that extended for 8 cm and was causing colorectal obstruction. This radiograph was taken 190 days after stent placement.

Esophageal neoplasia

Greater than 50% of human patients will have unresectable esophageal neoplasia at the time of diagnosis (Burstow et al. 2009). The median survival time for these patients is between 3 and 6 months, and palliative treatments are often pursued due to the grave prognosis (Sabharwal et al. 2005; Wilkes et al. 2007). The palliation of dysphagia is essential to the patient's quality of life, and esophageal stents are often placed in an attempt to achieve this goal (Sabharwal et al. 2005; Wilkes et al. 2007; Burstow et al. 2009). Esophageal stents have been shown to be an effective means of relieving malignant dysphagia secondary to malignant obstructions (Sabharwal et al. 2005; Wilkes et al. 2007; Burstow et al. 2009). Esophageal stenting for neoplastic obstruction has not been described in companion animals.

Biliary neoplasia

Obstruction of the biliary tree can occur from both primary hepatobiliary disease as well as external compression from other abdominal neoplasia (Moss et al. 2007; Lee 2009). While surgical bypass and the placement of both plastic and metal stents have been described in human patients, the endoscopic placement of metal stents is considered the treatment of choice (Moss et al. 2007; Lee 2009). However, metal stents can become occluded, and research toward developing drug-eluting stents to prevent occlusion and to deliver local chemotherapy is being conducted (Lee 2009). Biliary stenting for relief of benign obstructions (mostly pancreatitis) in dogs and cats has been described (Mayhew et al. 2006; Mayhew and Weisse 2008); however, reports on the relief of malignant obstructions with stents are lacking.

Percutaneous drainage

Malignant body cavity effusions

Interventional radiologists are often called on to relieve malignant effusions within the thoracic and abdominal cavities. In cases of malignant effusions, the goal of placing a catheter is palliation of the associated adverse clinical signs. The catheter may be placed temporarily or attached to an external or subcutaneous port for longer-term drainage. Placement of the drainage catheter does not treat the primary disease, and recurrence of the pleural or abdominal fluid may be rapid. Long-term placement of a catheter with a port may be indicated in many cases of malignant effusion.

Many interventional radiologists consider pigtail catheters placed with ultrasound guidance the gold standard when treating malignant effusions (Klein et al. 1995; Parulekar et al. 2001; Liang et al. 2009). In human patients with malignant thoracic effusions, small-bore catheters (such as pigtail catheters) have demonstrated similar outcomes when compared to large-bore chest tubes (Clementsen et al. 1998; Parulekar et al. 2001). Patients undergoing removal of thoracic effusions with small-bore tubes were also found to be more comfortable (Clementsen et al. 1998).

Recently, a modified Seldinger technique was used to place small-bore chest drains in the thorax to relieve effusions in dogs and cats (Valtolina and Adamantos 2009). While only 1 of 20 animals had a malignant effusion, the study revealed that these chest drains were placed easily and effectively by people with varying levels of experience (Valtolina and Adamantos 2009). Anesthesia was not necessary for drain placement in any of the cases, and 24 of 29 chest drains were placed in less than 10 minutes (Valtolina and Adamantos 2009).

Other drainages

Percutaneous drainage of the gallbladder and the percutaneous placement of nephrostomy tubes to divert urine flow may be indicated with certain neoplastic processes. Both ultrasound and fluoroscopic guidance have been used to place these tubes (Morgan and Adam 2001; Covey and Brown 2006; Saad et al. 2009; Uppot 2009). These techniques may be useful as temporary palliative measures to stabilize patients prior to a definitive surgery.

Minimally invasive placement of nephrostomy and cholecystostomy tubes is being performed in veterinary clinics, but reports are lacking. In a canine cadaver study,

pigtail catheters were placed in gallbladders using both ultrasound guidance and laparoscopic guidance, and the two techniques were compared (Murphy et al. 2007). The laparoscopic-guided technique was found to be significantly more likely to result in successful placement of the pigtail catheter (Murphy et al. 2007). Percutaneous biliary drainage has been shown to be safe and effective in humans (van Delden and Laméris 2008), and further investigation of these procedures in veterinary cases is necessary.

Tumor ablation

According to Simon and colleagues (2005), tumor ablation is "the direct application of chemical or thermal therapies to a tumor to achieve eradication or substantial tumor destruction." The most commonly used forms of tumor ablation include radiofrequency ablation, cryoablation, microwave ablation, laser ablation and intratumoral injection of compounds such as ethanol, hot saline, and acetic acid. Additionally, high-intensity focused ultrasound is showing promise in successful treatment of certain tumors, including prostatic neoplasia (Rebillard et al. 2008). These procedures can be performed with minimally invasive image-guided techniques. Multiple tumor types have been treated with ablation, and the research into the use of tumor ablation is vast and growing infinitely. Because many human tumors are diagnosed at a stage when resection is not possible, tumor ablation offers an alternative option for treatment, and this therapy may also benefit our veterinary patients.

Radiofrequency ablation (RFA) has been the most studied form of ablative therapy (Pentecost 2006). RFA can be performed with either monopolar or bipolar radiofrequency systems (Pentecost 2006). An electrical pole (or poles in biopolar systems) located on a probe is placed within the tumor tissue (Rose et al. 2006; Mahnken et al. 2009). Radiofrequency waves are converted to heat, and this thermal damage causes subsequent tissue destruction (D'Ippolito and Goldberg 2002; Kunkle and Uzzo 2008). Control of the area that is exposed to RFA is essential to prevent damage to surrounding normal tissue (D'Ippolito and Goldberg 2002). In human medicine, general recommendations for focal ablation with RFA are to aim for homogenous necrosis of the entire tumor as well as a surrounding region of normal tissue at least 1 cm thick (Rose et al. 2006).

Most clinical experience with RFA has been with treatment of hepatic malignancies, particularly hepatocellular carcinoma. Treatment of metastatic colonic disease has also been reported (Lencioni et al. 2009; Padma et al. 2009). RFA is considered by some as the treatment of choice for early-stage, nonresectable hepatocellular carcinoma (Lencioni et al. 2009). Across several studies, RFA has been shown to be an effective treatment modality for liver tumor destruction and results in an acceptable level of morbidity (Lencioni and Crocetti 2007). Other tumor types that are being treated with RFA include renal, pulmonary, and breast tumors (Noguchi et al. 2006; Rose et al. 2006; Abbas et al. 2009; Carraway et al. 2009; Raman et al. 2009; Vogl et al. 2009). RFA has been used to treat canine primary hyperparathyroidism (Pollard et al. 2001) and feline hyperthyroidism (Mallery et al. 2003), but the clinical use of RFA to treat malignant neoplasia in companion animals has yet to be investigated.

Cryoablation uses alternating freeze-thaw cycles that cause intracellular ice crystal formation, cellular dehydration, and microcirculatory failure, which results in ischemia and cytotoxicity (Vestal 2005; Raman et al. 2009; Vogl et al. 2009). Cryoablation is being successfully used to treat small renal masses, liver neoplasia, and prostatic neoplasia, as well as bone and soft tissue metastases in humans (Vestal 2005; Kunkle and Uzzo 2008; Callstrom and Kurup 2009; Padma et al. 2009; Raman et al. 2009). Improved outcome with decreased morbidity has been reported with the use of cryotherapy to treat prostatic neoplasia (Vestal 2005).

Microwave and laser ablation are newer ablation strategies, but the use of these systems is growing quickly as the clinical utility is being discovered. Microwave ablation works by heating the water molecules in tissues, with resultant coagulation necrosis and cell death (Simon et al. 2005; Abbas et al. 2009). Microwave ablation has been evaluated in the treatment of liver, lung, kidney, adrenal gland, and bone neoplasia in humans (Simon et al. 2005; Lencioni and Crocetti 2008; Moser et al. 2008; Abbas et al. 2009). Laser ablation is performed with a neodymium-YAG laser. This device elevates the temperature of tumor tissue and also results in coagulative necrosis (Vogl et al. 2009). Clinical reports of laser ablation are lacking, but proposed applications include liver, lung, and bone tumors (Pacella et al. 2001; Lencioni and Crocetti 2008; Moser et al. 2008; Vogl et al. 2009).

Percutaneous ethanol injection (PEI) with ultrasound guidance is a well-described technique for treating hepatocellular carcinoma but has also been used to treat other malignant neoplasia in humans (Lencioni and Crocetti 2008; Moser et al. 2008; Mahnken et al. 2009; Padma et al. 2009). Alcohol stimulates coagulation necrosis as it induces cellular dehydration and causes thrombosis-induced ischemia (Lencioni and Crocetti 2008; Moser et al. 2008; Mahnken et al. 2009). PEI has the advantage of low morbidity but may not cause complete tumor necrosis as the ethanol spreads