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Principles of Surgical Oncology

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Cancer treatment is a rapidly changing and evolving area involving 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 solid cancers 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. Surgeons trained in these programs have expertise in the selection of 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 what can be mastered within a three-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 almost 20 years. With the development of novel treatments, 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 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 prior to 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 the owner with enough information to help them make an informed choice regarding the best treatment pathway 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 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

Veterinary Surgical Oncology, Second Edition. Edited by Simon T. Kudnig and Bernard Séguin.

Companion website: www.wiley.com/go/kudnig/veterinary

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/Concomitant Disease

Staging diagnostics such as a complete blood count, chemistry profile, urinalysis, thoracic radiographs and abdominal ultrasound, and/or thoracic and abdominal computed tomography (CT) are essential components for the preoperative assessment of veterinary oncologic 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 in providing 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 anatomic 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/or 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 percent tumor necrosis) has been shown to be associated with increased survival. A 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 anatomic 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 with a view 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 (Seguin 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

The first decision in the surgical planning in removing a tumor is to determine the "surgical dose." The surgical dose refers to how aggressive the excision is with respect to the edges of the tumor. The surgical dose has been divided into: intracapsular, marginal, wide, and radical (Figure 1.1). An intracapsular excision is where the capsule of the organ where the tumor arises from (e.g. thyroid gland) or the pseudocapsule of the tumor (e.g. soft tissue sarcoma) is disrupted and the tumor is removed in pieces. A marginal excision is where the removal is done just outside or on the capsule or pseudocapsule. Oftentimes, the tumor is "shelled out." A wide excision is when the tumor and its capsule are never entered and grossly normal tissue surrounds the specimen. This is often defined as 2–3 cm of normal tissue around the edges of the tumor and one fascial place beneath the cutaneous and subcutaneous tumors. The 2–3 cm of normal tissue is in situ and not histological. A radical excision is the removal of the entire compartment

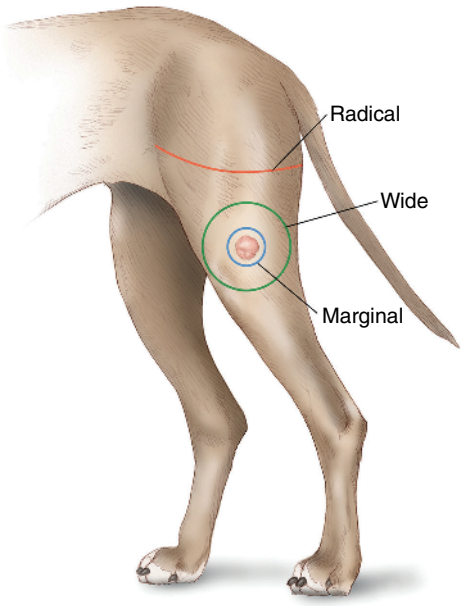

Figure 1.1 Diagram illustrating the different doses of surgery: marginal, wide, and radical being an amputation in this example. Intracapsular is not shown. *Source:* Illustrated by Molly Borman.

or structure where the tumor is arising from. An example of a radical excision is a limb amputation.

When removing a tumor, there can be three different goals: curative, palliative, and cytoreductive. These goals will dictate the dose of surgery and several factors will guide which goal should be pursued. The first factor is tumor type. Because benign tumors are limited to their capsule and do not extend into the normal-appearing tissues, a marginal excision is performed. Malignant tumors, however, have the ability to extend into the grossly normal-looking tissue at the microscopic level (Figure 1.2). Other factors need to be considered to determine the goal and consequently the dose of surgery. With (most) malignant tumors, when the goal is curative, a wide or radical

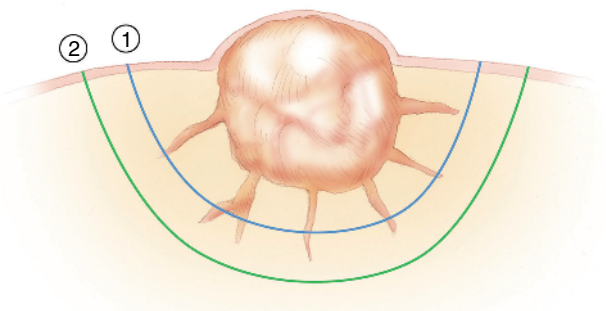

Figure 1.2 Diagram showing the extension of tumor into the grossly normal-looking tissue. These extensions are most typically at the microscopic level. This is the reason to perform a wide excision (2), as opposed to a marginal excision (1), with the goal to achieve a complete excision. *Source:* Illustrated by Molly Borman.

excision is required. For a palliative or cytoreductive goal, a marginal excision is performed. An intracapsular excision is rarely indicated.

The additional factors to consider to determine the goal of the surgery are: tumor size and location, stage of the cancer, overall health of the patient, risk of the surgery, prognosis, and goals of the owners. Table 1.1 provides examples of how these factors come into play, understanding there are always exceptions or nuances (see section on margins and palliative and cytoreductive surgery).

Because knowing the tumor type is essential in most instances, methods to get a diagnosis are a fine needle aspirate (FNA) or biopsy.

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 FNA is dependent on many factors including the tumor type, location, and amount of inflammation. Overall sensitivity and specificity of cytology have 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, an FNA of cutaneous or subcutaneous lesions can be obtained with no sedation and a minimal amount of discomfort. Fine needle aspiration has been compared to histopathologic samples in several studies. In one 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, and these numbers varied slightly based on tumor type (Ghisleni et al. 2006). For example, both the sensitivity and specificity were 100% for mast cell tumors (Ghisleni et al. 2006). In one study looking at the accuracy of cytology of lymph nodes in dogs and cats, cytology had a sensitivity of 67%, specificity of 92%, and accuracy of 77% for a diagnosis of neoplasia (Ku et al. 2017). In that study, 31% of metastatic lymph nodes secondary to a mast cell tumor were falsely negative (Ku et al. 2017). In another study evaluating the value of cytology of lymph nodes to detect metastasis of solid tumors, the sensitivity of needle aspirates of the lymph node was 67% for sarcomas, 100% for carcinomas, 63% for melanomas, 75% for mast cell tumors, and 100% for other round cell tumors. The specificity varied between 83 and 96%; also, 20% of nondiagnostic samples were metastatic (Fournier et al. 2018).

The goal of fine needle aspiration is to differentiate between an inflammatory or neoplastic process and, if

Table 1.1 Factors affecting the goal of surgery and consequently the dose of surgery

Tumor type	stage	Size	location	Owner's goals	prognosis	Overall health of patient	Goal of surgery	Dose of surgery
Benign								Marginal
Malignant	Metastasis present						Palliative	Marginal
	No metastasis	Small	Trunk		Good to excellent	Good	Curative	Wide
		Significant	Limb	Owners accept amputation	Good to excellent for function	Good	Curative	Radical
		Significant	Limb	Owners refuse amputation but accept surgeries with higher morbidity and risks	Good for local control and long term survival	Good	Curative	Wide (with reconstructive surgery)
		Significant	Limb	Owners refuse amputation or surgeries with higher morbidity and risks	Good with adjuvant therapy	Good	Cytoreductive	Marginal
						Significant co-morbidities	Palliative	Marginal

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 obtaining the FNA is to guide the staging diagnostics (where to look for metastasis or paraneoplastic diseases) and surgical dose. For example, an FNA of a mass showing normal adipocytes would indicate the mass is not inflammatory, rather it is a neoplastic process and it is benign (lipoma). Based on the knowledge of the biologic behavior of this tumor, no other staging tests would be performed and minimal surgical dose would be prescribed (marginal resection). Alternatively, if the FNA of a mass indicated carcinoma cells, more advanced staging (three-view thoracic radiographs, abdominal ultrasound and/or thoracic and abdominal CT, lymph node aspirates) would be indicated and a larger surgical dose would be prescribed.

Fine needle aspiration of internal organs can also be performed and may be helpful in guiding diagnostic and treatment choices. Image guidance should be utilized when obtaining FNAs 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). Cytologic 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 an FNA sample. Thymomas will contain both CD4+ and CD8+ lymphocytes, 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 utilized 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 one study, 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). In a more recent study, histology of a bone lesion was superior to cytology (Sabattini et al. 2017). Histology of a biopsy had a sensitivity of 72%, specificity of 100%, and accuracy of 82%, whereas cytology had a sensitivity of 83%, specificity of 80%, and accuracy of 83% (Sabattini et al. 2017).

As with any procedure, FNAs 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 FNA 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 brings the risk to cause 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 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 histopathologic interpretation. Because of this, two major categories of biopsy have been designated: pretreatment biopsy (tissue obtained before treatment initiation) or posttreatment biopsy (tissue obtained at the time of definitive tumor resection). All biopsy procedures, whether pretreatment or posttreatment, should be carefully planned with several factors in mind. These factors include known patient comorbidities, anatomic location of the mass, differential diagnoses, biopsy technique, eventual definitive treatment, and any neoadjuvant/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 may not need general anesthesia.

Instrumentation includes a needle core biopsy instrument (automated or manual) (Figure 1.3), #11 scalpel blade, local anesthetic, and a 22 g 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 bupivacaine. 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 g 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 (most commonly ultrasound) 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

This 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.

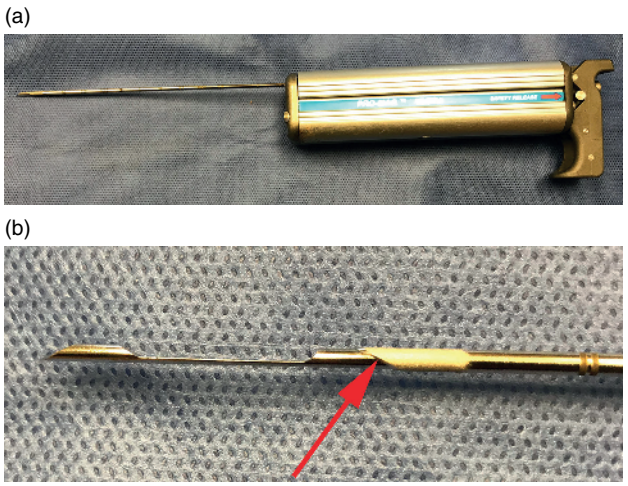

Figure 1.3 (a) Automated needle core biopsy instrument. (b) The tip of the needle has an indentation, which is filled with the tumor tissue when inserted. There is a sleeve with a cutting edge (red arrow), which cuts the piece of tissue in the indentation of the needle.

Instrumentation includes a punch biopsy instrument (Figure 1.4), which typically comes in sizes of 2, 4, 6, and 8 mm; #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 bupivacaine. For cutaneous masses, an incision is not necessary. For subcutaneous masses, make an incision in the skin over the mass and dissect tissues overlying the mass if present to allow for the procurement of a better sample. 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, utilize 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

This technique is effective for masses in all locations and generates a larger sample for histopathologic 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

Figure 1.4 Punch biopsy instrument, 8 mm in diameter.

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. The most important principle to consider is to obtain a representative sample of the mass. It is also important to obtain a sample that is deep enough and 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 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 incisions made in a parallel direction 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 a suture.

Excisional Biopsy

The approach to an excisional biopsy is variable 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, an FNA 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 or absence of knowledge of the tumor type remains after fine needle aspiration (e.g. nondiagnostic results from cytology), 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 wide excision. If it is deemed that an excisional biopsy can be performed while leaving this option, an excisional biopsy can be considered. For example, a 1 cm in diameter mass on the trunk of a large breed dog can be interrogated by excisional biopsy, whereas a 1 cm in diameter mass on the distal extremity of a dog should be interrogated by incisional biopsy (wedge or punch).

Once an excision is performed, the local anatomy is forever altered, tissue planes both deep and wide to the tumor are invaded, providing an opportunity for the 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 (lipoma), this margin is minimal or even intralesional. In other cases (soft tissue sarcoma), the margin should be 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 anatomic 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 utilizing 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. Although a more recent study suggests bone biopsies with a Jamshidi needle are only 82% accurate (Sabattini et al. 2017), an earlier study found that 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 #11 blade and a Jamshidi needle (Figure 1.5). 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.

For lesions that are large enough to be palpated, image guidance is not necessary. However, for small nonpalpable lesions, image guidance is recommended to document that the biopsy samples were indeed acquired from the lesion, preferably the center of the bone lesion. Fluoroscopy and

radiography can be used and sometimes even CT-guidance can be helpful.

Lymph Node Biopsy

Treatment and biopsy of lymph nodes in neoplastic disease remain controversial (Gilson 1995). It is demonstrated that lymph node size (Langenbach et al. 2001; Williams and Packer 2003) and needle aspirates are not great at detecting metastases (Ku et al. 2017; Fournier et al. 2018). Removing a lymph node or performing an incisional biopsy of a lymph node can aid in staging the patient and assist in the determination of prognosis or treatment options. The surgical oncologist should have a thorough knowledge of the anatomic location of the probable draining lymph node for a mass in a particular location. Alternatively, sentinel lymph node detection techniques such as lymphography and scintigraphy can be used (see Chapter 14). The excisional biopsy of superficial lymph nodes such as the mandibular, superficial cervical (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 #10 or #15 blade, Metzenbaum scissors, forceps, Mayo scissors, and suture. 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 and/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. Many "lymph nodes" are actually lymphocenters. The implication is that multiple lymph nodes can be present in one location, for example, the mandibular lymphocenter often has two to three lymph nodes.

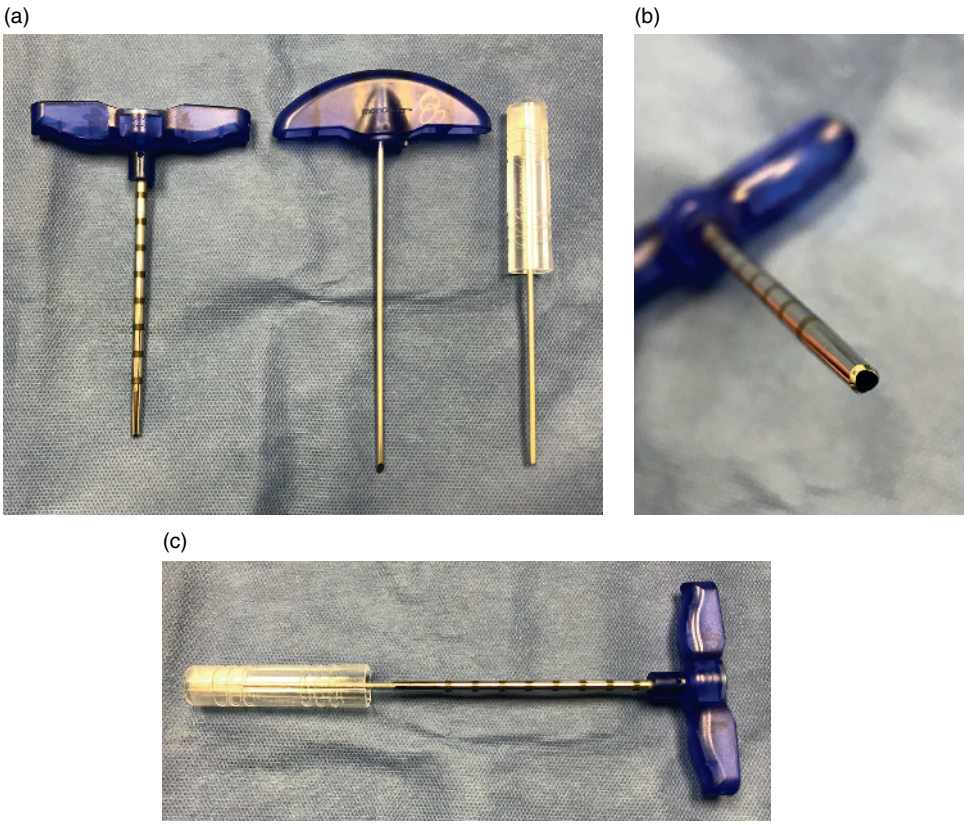

Figure 1.5 (a) Jamshidi needle (left) with the two stylets (middle and right). The stylet in the middle is used to approach the bone. The stylet to the right is used to remove the sample from the needle after being acquired. (b) The end of the needle is tapered, helping to keep the sample in the needle when the needle is removed from the bone. (c) To remove the sample from the needle, the stylet is introduced through the tip of the needle and the sample is pushed to exit the base at the handle. In some instances, there is too much resistance to push the sample out of the handle end, in which case the first stylet is used to push the sample out through the tip. It is not ideal because in theory the sample can suffer some damage going through the narrowed end, but sometimes it is necessary.

Endoscopic Biopsy

Esophagoscopy, gastroscopy, duodenoscopy, and colonoscopy are routinely performed in veterinary medicine as minimally invasive techniques to attain biopsies of the gastrointestinal tract. Biopsies attained during these procedures are generally smaller than what 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 underutilized modalities, but successful procurement of kidney, bladder, liver, spleen, adrenal gland, pancreas, stomach, intestine, and lung biopsies have been described by the 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; Steffey et al. 2015; Lim et al. 2017).

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 attempt to not contact 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); however, tension-relieving skin incisions are contraindicated after removal of a neoplasm. 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 that 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 *en bloc* 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 important that a new set of instruments, gloves, and possibly drapes be utilized 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 there to be 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.

There is considerable confusion and controversy surrounding the issue of appropriate surgical margins and clinical decision-making when histologically incomplete

margins are obtained. Prior dogma has suggested that an overly generous margin is likely to be curative. In order to ensure a good oncological outcome, surgical oncologists have been trained to be as aggressive as possible. While it is well-accepted that aggressive surgical margins tend to lead to better local control, this is not true in every case. Even extensive, complete surgical margins do not always lead to a cure. Local recurrence and/or metastasis may occur despite a histologically complete margin. Mounting evidence in the human sarcoma literature seems to suggest that a planned and executed "widest" surgical margin has not resulted in sufficient improvements in disease-free intervals to justify the morbidity incurred with such resections. This opinion among human surgeons is confounded by the routine use of adjuvant radiation therapy in traditionally difficult-to-resect tumors such as extremity sarcomas. In veterinary medicine, adjuvant radiation therapy may not be available or affordable. As we know from experience and from the veterinary literature, not every patient with a histologically positive margin will experience recurrence. To confound things further, different malignancies and grades of malignancy (mast cell tumor vs. soft tissue sarcoma, low grade vs. high grade) may require specific and separate guidelines for margin planning.

Veterinary surgical oncology has traditionally followed the adage that for *most* malignant solid tumors, a 2–3 cm surgical margin and an additional tissue plane deep is the desired intraoperative goal to achieve wide excision, and is most likely to result in a histologically clean excision. Nonetheless, many surgical oncologists bend these "rules" based on tumor-specific evidence in the literature and personal experience. Examples of this include using proportional margins in mast cell tumor resection (Pratschke et al. 2013) or less generous margins for specific anatomic areas, where 2–3 cm could result in undesirable functional morbidity (e.g. head and neck, spinal column). Many, based on experience, feel comfortable with smaller margins in specific tumor types (anal sac tumors, thyroid tumors, low-grade sarcomas) and in some cases, this is supported in the veterinary literature by findings of no difference in local recurrence between one "width of margin" and a lesser one. However, the minimum safe distance necessary to reduce the chance of local recurrence is currently unknown. Regardless of what is actually performed in the operating room, most of the published literature agrees that a histologic margin free of tumor cells is considered the best predictor of improved local recurrence.

Varying Definitions of "Margin"

There are several considerations that make the comparison of evidence in the literature and subsequent adjustment of surgical planning difficult. There are distinct and widely different concepts of what constitutes the definition of a "margin" and how the quality or magnitude of margins are reported. Margins may refer to: (i) the intraoperative margin (i.e. the normal tissue margin as measured in situ between palpable tumor and the planned incision), (ii) the width of normal tissue beyond palpable tumor and the resected edges as measured after resection and before fixation, (iii) the measured width of tissue beyond the palpable tumor after fixation, and (iv) the measured width of normal tissue between the nearest microscopic tumor cell and the resected edge as seen by a pathologist on the slide. Each of the above margin assessment methods represents very different measurements, yet it is rare for veterinary journal articles to report *which* of these margin assessment methods is being used or even the *magnitude* of the resected margin beyond a description of "wide," "marginal," or "incomplete." A recent study (Terry et al. 2017) showed that there was significant difference in the measured grossly normal surgical margins following sarcoma removal after resection compared to the planned intraoperative excision margin. Therefore, surgeon intent (wide or marginal) should not be considered an acceptable means of reporting margins obtained. In addition, these same authors noted that comparison of subgross evaluation of tumor-free margins, once sectioned and placed on a slide, was not at all comparable to the magnitude of the pathologist-reported histological tumor-free margin.

In human medicine, there has been a shift in margin assessment schemes from a traditional Enneking-style margin assessment (intralesional, marginal, wide, or radical) to either a distance method (reporting the minimum distance between the nearest observed tumor cell and the inked surgical margin) or a qualitative method, where resected specimens are classified as R0 (no tumor at the inked edge), R1 (microscopic tumor at the inked edge), and R2 (residual gross disease left in patient). This highlights the important difference between surgical margins in situ versus histologic margins. Recent reports comparing the distance method to the qualitative method indicate that with osteosarcoma the distance method in combination with tumor response to chemotherapy (>90% or <90%) was the best predictor of local recurrence (Cates 2017). Conversely, in soft tissue sarcomas of the extremity, the qualitative assessment was most predictive and the distance method was not (Harati et al. 2017). It is likely, therefore, that different methods of margin assessment will have differing prognostic significance in veterinary surgical oncology.

The Influence of Sectioning

Despite histopathology universally being used to assess the completeness of surgical margins, the methods of

sectioning to evaluate the completeness of margins may vary. The most common method is to perform four complete radial sections. These represent cranial, caudal, dorsal, and ventral portions of the submitted specimen. Unless the surgeon uses tissue ink to identify the surgical margin, it may be difficult for the pathologist to determine whether any one of these sections represents a surgical margin or a trimming artifact. Tissue inking improves the likelihood that the standard sections evaluated do indeed represent true surgical margins; however, in the case of radial sectioning, the area of margin examined represents only a small percentage of the actual surgical margin surface. Several reports document the fact that with more sections, there is a higher likelihood of finding a positive margin. Comprehensive margin evaluation of a 1 cm cutaneous malignancy is estimated to require greater than 4000 sections, making this an impractical means of assessing margin completeness. Tangential sectioning is an alternative method to evaluate surgical margins. Tangential sections are taken parallel to the inked edge, and represent a potentially more sensitive method to detect residual tumor at the margin because they evaluate a greater percentage of the total margin. In humans, significant differences were noted in margin reporting outcomes when tangential sectioning was compared with radial methods. The disadvantage to tangential sectioning is that it does not allow for quantification of the histologically tumor-free distance and lacks contextual reference to the primary tumor. In one recently reported study in the veterinary literature (Dores et al. 2018), tangential sections detected a significantly higher proportion of positive margins as compared with radial sections in resected mast cell tumors. In this study, radial sections incorrectly classified 50% of the margins as being complete. Surgical oncologists should therefore understand the histologic margin status is influenced not only by the adequacy of excision but also by the method of margin assessment.

Future Directions

The quality of the margin may be more influential than the quantity. Tissue barriers such as muscle, fascia, joint capsule, cartilage, and bone are inherently resistant to tumor penetration. Most solid tumors expand within their tissue of origin initially and grow along lines of least resistance. Surgical oncologists understand that including a tissue barrier beyond where the tumor is attached will trump a larger tissue margin in the absence of that barrier in terms of the likelihood of obtaining complete margins. However, fascia, often favored as a good tissue barrier and easily identifiable to the surgeon, is frequently difficult to discern as a distinct structure on histological sections. This creates difficulty in margin interpretation especially when minimum distances between the fascial plane used as a surgical margin and the nearest tumor cell exist. Is the patient at higher risk for recurrence with a 2-cm histologic margin of normal fat or a 2-mm histologic margin of normal tissue that includes a defined fascial layer (per surgeon reporting)?

Human medical evidence has suggested that qualifying the peripheral growth pattern of sarcomas as either "pushing" (no infiltration into surrounding tissue beyond the pseudocapsule) or "infiltrative" (tumor pseudocapsule poorly defined or satellite nodules present) was predictive of local recurrence (Engellau et al. 2005, 2007). The "pushing" contour was seen most commonly in low-grade sarcomas, but a significant percentage of high-grade sarcomas also displayed this characteristic (Engellau et al. 2007). High-grade tumors with a "pushing" growth pattern had significantly fewer local recurrences than high-grade tumors with "infiltrative" growth patterns (Engellau et al. 2007; Lintz et al. 2012). It is therefore possible that in even high-grade sarcomas, a pushing pattern of peripheral growth may allow a narrower resection than a tumor with an infiltrative contour. These features (pushing or infiltrative) can be seen on MRI (Iwata et al. 2014; Nakamura et al. 2017), making it conceptually possible to plan resection margins preoperatively based on tumor contour features; however, this approach has not been studied extensively in human medicine or at all in veterinary medicine.

Compartmental tumor excision has been proposed by Enneking and others as a means to diminish the risk of local recurrence in musculoskeletal sarcomas. In compartmental excision, an entire compartment of tissue is removed, for example, an entire muscle or muscle group, as opposed to circumferentially resecting *en bloc*. Proponents argue that wide local excision, involving an arbitrary measure of a normal tissue "cuff," risks leaving satellite nodules beyond the resected plane, especially in high-grade, infiltrative tumors. Indeed, compartmental tumor excision has been shown to reduce recurrences in some tumor types and may be worth considering adopting in veterinary surgical oncology.

Currently, the best-known predictors for local recurrence of solid tumors are histologic grade and completeness of excision. These features are typically assessed after resection, although grade may be determined prior to resection if the tumor is biopsied and sufficient tissue can be evaluated. Newer technologies such as genome sequencing and proteome analysis are designed to probe deeper into the biological aggressiveness of an individual tumor. Utilization of these methods may provide more specific information, can be acquired prior to surgery, and will provide information from both the tumor and the surrounding

microenvironment. The microenvironment/tumor stroma is becoming a featured player in the understanding of tumor biology, as scientists begin to understand the importance of a permissive microenvironment and its role in invasion and metastasis. These datasets may ultimately provide the most accurate assessment of biologic behavior and subsequently assist the surgeon in personalized surgical planning. These analyses may prove to be far more predictive of both local recurrence and metastatic potential than histologic grade.

Given the myriad factors that influence assessment and reporting of surgical margins, it stands to reason that surgical oncologists need to collaborate with pathologists to standardize margin reporting and continue to assess the most predictive prognostic factors within each specific tumor type. It may be that the distance method is better for predicting recurrence in one type or grade of tumor, whereas in a different tumor type, the qualitative method may be most predictive. It is imperative that surgeons understand the limits and advantages of various methods of tissue sectioning and margin interpretation, and continue to develop new means of assessing biological aggressiveness. A one-size-fits-all approach is no longer the best medicine.

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 function issues. 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 colors are considered the best to use while red, violet, and green are less ideal (Seitz et al. 1995; Milovancev et al. 2013).

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 for more complete fixation (Dernell and Withrow 1998; Ehrhart and Powers 2007). However, when slicing a large specimen, care should be taken not to slice through the surgical margins but rather leave those untouched. Therefore, the slicing is done through the skin into the tumor for cutaneous or subcutaneous tumors. 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 (Kaufman et al. 1986; Lessells and Simpson 1976). 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 nonneoplastic diseases in 93% of cases (Whitehair et al. 1993).

Wound Healing

The veterinary oncologic 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 like tumor type and completeness of surgical excision have to be considered as well. Neoadjuvant/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) (see Chapter 2).

Proper surgical techniques, as described above, can be employed to decrease the chance of wound complications. Regular communication with the patient's agent 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 adjuvant 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 agent 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 et al. 1986a, b) (see also Chapter 2). By the time a patient is ready for suture/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 given 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 will 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 the 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 remains adaptive. It is hopeful that the desire for improved outcomes will continue to improve the lives of our patients as well as their agents. Prolonging a quality of life for veterinary patients and advising their agents appropriately about the options that we have to offer should remain our goal as advances in therapy occur.

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