Role of Surgery in Multimodal Cancer Therapy for Small Animals

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KEYWORDS

• Surgical oncology • Resection • Adjuvant therapy • Chemotherapy • Radiation

KEY POINTS

- Surgery is an essential component of the diagnosis and treatment of cancer in small animals.
- The method of biopsy and of tumor removal can have a significant impact on outcome.
- Once a diagnosis is made and the patient is staged, the dose of surgery and timing of adjuvant therapies should be planned by the oncology team before initiating any therapies.
- It is critical that the surgical oncologist has a good understanding of the impact of chemotherapy and radiation on surgical patients and that the surgical site is treated appropriately if postoperative radiation is part of the multimodal plan.

Surgery is the mainstay in the diagnosis and treatment of most solid tumors in small animals. It can be used as sole therapy in some situations, but often is used in concert with adjuvant therapies such as chemotherapy and radiation. It is critical that the surgical oncologist has a good understanding of surgical oncology principles; cancer biology; and the roles of surgery, radiation, chemotherapy, and novel therapies in treating neoplasia. The methods of biopsy for diagnosis and staging are often at least in part the responsibility of the surgeon and can have a considerable impact on patient outcome. A qualified surgeon has the technical ability to perform complicated procedures; however, the skill of selecting the best procedure that compliments an integrated plan for cancer treatment is what differentiates a general surgeon from a surgical oncologist.

Disclosures: None.

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Vet Clin Small Anim 44 (2014) 855–870
http://dx.doi.org/10.1016/j.cvsm.2014.05.008 **vetsmall.theclinics.com**
0195-5616/14/$ – see front matter

PREOPERATIVE EVALUATION

The initial task of the surgeon is to obtain a diagnosis. The first step in this process often involves a fine-needle aspirate, and, although this is a recommended step in getting a diagnosis, cytology is prone to inaccuracy because the pathologist receives a small sample of cells lacking in vivo orientation. Before a major surgical procedure, a histologic diagnosis is recommended. The suitable type of biopsy may be a Tru-Cut, incisional, or excisional biopsy, and the decision making behind which biopsy technique is most appropriate varies with the size, location, and presumptive or cytologic diagnosis of the mass. Regardless of the method of biopsy, the biopsy tract must be resected with the definitive resection and the biopsy incision should be oriented to facilitate this. In addition, the tissue planes surrounding the mass must not be disrupted by the biopsy procedure. A solid mass should not be removed without knowledge of the tumor type (an unplanned excision). Unplanned excisions are often associated with an excision that is larger than is necessary to remove the gross disease only, but not large enough to remove all microscopic disease. In addition, the unplanned excision has the potential to disrupt the surrounding fascia and may be oriented in a manner that makes reexcision challenging.

Staging for local and distant extent of disease is critical before surgical planning. The staging performed depends on the suspected or confirmed tumor type. Three-dimensional imaging is useful in screening for occult metastatic disease, although availability and costs can limit its use. It is difficult to generalize about the appropriate method for staging solid tumors, but computed tomography (CT) scan of the mass, thorax, and possibly the abdomen for local and distant staging and incisional biopsy of the mass after evaluating the images is a highly efficient way to obtain a lot of information about the extent of disease and a definitive diagnosis. Surgical staging may also involve surgical removal or biopsy of local lymph nodes, which may be combined with initial diagnostics or definitive resection. Various aspects of initial staging can be performed using minimally invasive techniques, which may reduce overall morbidity associated with tumor staging.

SURGICAL TREATMENT

Once the histologic diagnosis, grade, and extent of disease are known, a surgical plan can be made based on the predicted biological behavior of the disease and the owner's goals for therapy. A comprehensive plan that takes into account the need for and the timing of adjuvant therapy should be developed before a surgical intervention. The goals of surgery may be palliative or curative.

The difference between palliative and curative intent treatment is not always clear, and these goals can be thought of as a continuum, rather than as absolutes. However, in general terms, palliative-intent surgery is intended to achieve cytoreduction of the tumor to relieve clinical signs, improve the patient's quality of life, and/or to allow adjuvant therapies to have the greatest impact on residual disease. Often palliative surgery is performed when local and/or metastatic control is not possible. Palliative surgery may be intralesional, in which gross disease remains, or preferably marginal, in which all macroscopic tumor burden is removed, if possible. Another goal of palliative surgery is a tension-free closure that heals with minimal complications. These goals should be balanced when deciding between an intralesional versus a marginal excision.

Surgery may also play a role in palliation when metastasectomy is performed. Guidelines for pulmonary metastasectomy have been reported in human oncology. CT scan is used to monitor metastatic lung nodules; the number of nodules, disease-free interval, and tumor doubling time are important factors in decision making.[1–4] In veterinary

oncology, pulmonary metastasectomy for the management of canine osteosarcoma was reported by O'Brien and colleagues[5] in 1994. Disease-free interval between local control of primary appendicular osteosarcoma and the appearance of lung metastasis and the number of nodules were prognostic. Liptak and colleagues[6] also reported pulmonary metastasectomy in 4 dogs with osteosarcoma for the management of hypertrophic osteopathy. Because these studies were performed using radiography to evaluate the lungs for metastasis, reassessment of these recommendations using CT scan would be useful. Another change in veterinary surgery since the publication of this article is the increasing use of thoracoscopy to remove lung lesions, which may be more palatable to some owners compared with thoracotomy.[7,8] In veterinary medicine, metastasectomy is routinely performed in cases of canine anal sac adenocarcinoma, for which cytoreduction by extirpation of the iliolumbar node bed along with resection of the primary anal sac adenocarcinoma has been shown to lead to prolonged survival times with adjuvant chemotherapy.[9,10] Further, the presence of lymph node involvement has not been shown to have a negative impact on survival time if the nodes are removed as part of the surgical treatment.[10]

SURGICAL ONCOLOGY PRINCIPLES

Curative intent or definitive surgical therapy has the goal of local control of the tumor. Some tumor cells have the ability to break free from the parent mass and infiltrate the surrounding tissues, establishing microscopic satellite neoplasms. Often these leader cells cannot be seen grossly, but presumably they are there with certain types of tumors because of the high rates of local recurrence with marginal excision and because of evidence of infiltrative cells at histologic margins when a wide excision is not performed. The existence of these infiltrative cells has led to the dogma that malignant tumors must be resected with a wide or radical excision to achieve local control. A wide excision involves 2-cm to 3-cm radial margins and a fascial layer deep to the tumor, which is best planned with three-dimensional imaging. Fascia is used as the deep margin because it serves as a barrier to most tumor cells, which tend to infiltrate to, but not through, the fascia under the tumor (a notorious exception to this is the sarcoma cells of feline injection sites, for which even larger margins of 5 cm radially and 2 fascial planes deep are recommended[11]). The fascial plane that is used depends on tumor location; it may be true fascia overlying a muscle if it is possible to remove it from the muscle as a contiguous sheet. The fascial layer may also be the muscle, bone, or the chest wall, depending on tumor location. The tumor pseudocapsule, subcutaneous tissue, and fat cannot be considered a fascial plane and cannot be used as a deep layer in curative intent tumor resection. One uncommon exception to this guideline is in obese patients, for whom metric margins of 3 cm can be taken around the mass, including the deep layer. In these cases, a large metric margin may be sufficient as a deep margin. When the surgical margins are reported by the pathologist, the radial margins should be reported as a metric margin and the deep layer should be reported with the quality of the margin and not the metric distance. Radical excision involves the resection of an anatomic compartment in cases in which curative intent surgery is the goal, but cannot be achieved with a wide resection.

Intraoperative principles of surgical oncology are followed to minimize the risk of potential neoplastic cell contamination of areas beyond the tumor bed. Surgical instruments and gloves should be changed when shifting sites or masses during biopsy or excision. Within 1 tumor resection, different gloves and instruments must be used when harvesting a skin graft or flap for reconstruction. When dirty margins are anticipated during marginal resection, changing gloves and instruments for closure

is unlikely to result in a different outcome. When a wide or radical resection is performed and clean margins are anticipated, changing gloves and instruments for closure is also unlikely to change the outcome, even with dirty margins. If the tumor capsule is inadvertently entered during resection, the site should be closed with suture and lavaged with copious amounts of saline. Gloves and instruments should be changed and the surgery should continue with larger margins than originally planned. This unfortunate occurrence is rare and can be prevented by careful surgical planning using three-dimensional imaging.

Drains should be used judiciously in surgical oncology. Prevention of seroma formation is important because seroma formation can lead to contamination of the tissues surrounding the tumor bed with neoplastic cells if there is a marginal excision and/or dirty margins and it can be difficult to accurately treat this area with reexcision or radiation therapy. The use of gravity-depending Penrose drains should be avoided in general because they require that the drain is tunneled from the tumor bed to a distant ventral site. With dirty margins, contamination of the drain tract results in the need either to resect this tract or treat it with radiation, which can prove difficult. A Penrose drain can be used if the egress site can be optimized. However, closed-suction drains have several distinct advantages, the most important of which is that the exit point can be adjacent to the primary incision and that this drain site can easily be included in a future resection or radiation field if necessary.

ROLE OF THE HISTOPATHOLOGIST

It is essential that critical information is transferred from surgeon to pathologist and back to the surgeon. The history, gross description, and inking of surgical margins assist with accuracy of the histopathologic diagnosis and margin assessment. Painting the entire specimen with tissue ink results in random margin assessment. Margins of concern should be inked with a different color and the pathologist should be alerted. Otherwise, the cranial, caudal, ventral, and dorsal margins should be inked, as well as the deep margin. The deep margin should be inked directly under the main mass because this is the location where the cells are most likely to have invaded the underlying fascia. The pathologist's report should include a complete description that would allow another pathologist to report a diagnosis, grade, and margin assessment without seeing the slides.[12] The surgeon should read the entire report, paying particular attention to the number of mitotic figures, amount of necrosis, invasion into lymphatic and blood vessels, and degree of differentiation.

A disadvantage of histopathology as a method of margin assessment is the delays caused by tissue processing. During surgery, frozen section is uncommonly performed in veterinary medicine to assess margins, largely because of lack of availability and lack of training of veterinary pathologists in these techniques. These procedures also result in the loss of diagnostic material for fixed histopathology. A new technique in human surgical oncology that may be feasible in veterinary medicine is imprint cytology, or touch-prep evaluation, of surgical margins during surgery. The sensitivity and specificity of intraoperative imprint cytology compared with definitive margin evaluation in human patients having breast cancer lumpectomy has been reported to be 97% to 100% and 99% to 100%, respectively.[13,14] Although not yet evaluated in veterinary surgical oncology, advantages include a rapid procedure that does not require additional equipment or training if cytologist support is readily available. Further, the diagnostic material from the main specimen is not lost. Another novel technique for the real-time evaluation of the surgical margin is the intraoperative assessment of the tumor bed for residual neoplastic cells using a fluorescent probe and imaging

device. In the only report of this technique in dogs with soft tissue sarcoma, the histologic surgical margins correlated with the intraoperative results of the imaging device in 9 out of 10 cases.[15]

CHEMOTHERAPY AND SURGERY

In general, chemotherapy is indicated as adjuvant therapy in solid tumors in which the potential for metastatic spread is greater than 50%. The most common scenario in veterinary medicine when surgery and chemotherapy are both part of the treatment plan is that surgery is performed first and adjuvant chemotherapy is administered 10 to 14 days later, usually at the time of suture removal. The advantages of this approach are that it limits the potential for chemotherapy to have an effect on wound healing or to compound the effects of surgical complications such as infection. The other advantages of removing the tumor before chemotherapy is that surgery is performed sooner, which may improve quality of life in some patients, and that this allows time for the histopathology to be reported, which may be helpful in developing the overall plan for the patient going forward.

Most chemotherapeutic agents do not influence surgical wound healing; however, high-dose corticosteroid administration delays the inflammatory phase of wound healing and nonabsorbable or slowly absorbable sutures should be used. Skin suture removal should be delayed until healing is complete. Other information on the effect of chemotherapy on wound healing is sparse. In rat models, there is evidence that doxorubicin administration has an effect on wound strength when it is administered within 7 days before surgery. This effect seems to be mitigated when the drug is administered 14 days or more before surgery.[16–18] Another study using a wound model in rats also showed a significant decrease in wound strength when doxorubicin was administered up to 21 days after a wound was created, with this effect being mitigated when chemotherapy was delayed until 28 days after wounding, indicating that postoperative adjuvant chemotherapy may also have an impact on surgical wound strength.

If neoadjuvant chemotherapy is being considered, another practical reason to postpone surgery for a period after chemotherapy administration is the nadir (the lowest value of the blood cell count [neutrophils and/or platelets] after chemotherapy administration). It varies depending on the chemotherapy drug administered, but is usually 7 to 21 days after administration. Surgeons must be aware of the chemotherapy protocol that their surgical patients are receiving and the nadir of each of these chemotherapeutic agents, which is important for planning the timing of surgery and also when managing any postoperative complications while a patient is on chemotherapy. Before taking a patient having chemotherapy to surgery, a complete blood count (CBC) must be performed to ensure that it is safe to do so. If the cell counts are too low, supportive care should be given as needed and the CBC should be monitored until recovery.

The use of neoadjuvant chemotherapy is rarely reported in veterinary medicine. Although chemotherapy is not considered to be most effective against bulky disease, neoadjuvant chemotherapy been reported in human oncology to facilitate resection and often limb salvage in cases of osteosarcoma and soft tissue sarcoma.[19,20] In veterinary medicine, neoadjuvant chemotherapy has been considered to facilitate resection in a small number of reports. Large mast cell tumors in dogs can present a surgical challenge and neoadjuvant prednisone has been reported to enable resection; however, the recurrence rate in this study was 23.8%,[21] which suggests that neoadjuvant prednisone facilitates a marginal resection, but may not allow complete removal

of the mass. This strategy might be most effective when cytoreduction is the goal of surgery. Prednisone is likely to decrease the size of the tumor caused by inflammation, but does not change the infiltrative pattern of the malignant mast cells within the tumor bed. Neoadjuvant chemotherapy with toceranib and cytotoxic chemotherapy have been anecdotally reported for mast cell tumors in dogs, but no data on its efficacy exist.

Neoadjuvant doxorubicin has been reported in dogs with nonresectable subcutaneous hemangiosarcoma and, in 4 of 18 cases, the tumor response led to complete tumor resection. However, these patients did not have an improvement in survival time.[22] Neoadjuvant carboplatin has also been reported in dogs with appendicular osteosarcoma, with no difference in survival time between dogs given neoadjuvant versus adjuvant chemotherapy and limb amputation.[23] Neoadjuvant chemotherapy's most useful application may be in cases of solid tumors that are not resectable and in which a partial response may facilitate marginal or complete resection.

Nonsteroidal antiinflammatory drugs and low-dose, continuous chemotherapy, also known as metronomic chemotherapy, have recently been used in veterinary oncology to treat a variety of neoplasms through modulation of T-lymphocyte populations and antiangiogenesis. Small molecule inhibitors (tyrosine kinase inhibitors) are also being used with increasing frequency. Because of the antiangiogenic effects of both classes of medication, especially with the small molecule inhibitors, the risk of adverse effects on wound healing is significant. Animals receiving single-agent toceranib or imatinib therapy should have the drug withdrawn for a minimum of 1 week before performing surgery. Continuing the drug rest for a minimum of 2 weeks during healing seems prudent because most neovascularization is attenuating in wound healing after 2 weeks. Complex, difficult, and high-risk wounds should probably be rested from these drugs until healing is satisfactory as judged by the surgeon.

COMBINING RADIOTHERAPY WITH SURGERY

Radiation can be combined with surgery as a second local treatment of the management of neoplasms.[24] Radiation therapy (radiotherapy) can be administered systemically, internally, or externally. High-energy photon teletherapy (x-rays and gamma-rays) passes through tissues regardless of tissue density. In contrast, radiation with electron teletherapy can be delivered to a partial thickness of a body part, thereby sparing critical deeper structures. Photon and electron teletherapy can be combined. Partial-thickness penetration is useful for intraoperative dosing of radiation so that a high locally targeted dose is delivered once during surgery. After surgery, high-energy photons (fully penetrating) are administered to boost the dose to the target while minimizing the dose to normal tissue.

Teletherapy is usually delivered from linear accelerators (LINACs) or cobalt sources. Both can deliver state-of-the-art x-ray or gamma radiation, respectively, but LINACs are more versatile because the source can be moved and the beam can be manipulated by a variety of collimators. Radiation oncologists plan the treatments and work with radiation physicists and technologists for radiation delivery. Multiple factors are considered, including neoplasm size/density, location, nearby risk structures, local tissue health, depth of dose needed, total dose needed, and risk of early and late treatment effects.

Stereotactic radiosurgery (SRS) is a treatment variant usually reserved for small neoplasms (<3 cm) with precise margins. SRS is typically performed in the brain or spinal cord in lieu of surgery. Precise administration of a single high radiation dose is the defining feature of SRS. Stereotactic body radiation treatment (SBRT)/stereotactic

radiation treatment (SRT) is similar and the term is applied to non–central nervous system sites. SBRT delivers higher total doses through use of multiple fractions, but uses fewer fractions (usually <5) than conventional radiotherapy. The primary advantage of SRS/SBRT/SRT is that a high dose of radiation can be administered to a precise target, with a sharp decrease in the radiation dose to the adjacent tissues.

Although usually administered through the skin, radiation also can be delivered during surgery with intraoperative radiation therapy.[25] The surgeon exposes and isolates the target field with a sterile, transparent overdrape. A single high radiotherapy dose is delivered to the exposed tissue. The wound is closed and after surgery and additional radiation treatments are delivered with external doses. The advent of stereotactic radiation treatment has decreased the need for intraoperative radiation therapy, because the tissues can be spared from the radiation field through precise administration, rather than by surgical isolation.

Deciding whether radiotherapy should follow surgery is not difficult. Because of their complimentary nature as local treatments, sequential application of surgery and radiation should be considered whenever the application of either modality alone seems unlikely to effect a cure. Because both surgeon and radiation therapist must be aware of diagnosis and grade as well as volume, location, stage, and anticipated behavior of a neoplasm, the sequencing plan should be discussed before either treatment is initiated. The discussion is important because although these treatments are complimentary, they also can complicate one another.

Surgery alone is most effective as a treatment of neoplasms that are well defined and located in body regions where normal tissue can be removed with and encapsulate the neoplasm, the so-called margin, and still have sufficient tissue for local reconstruction. If the surgeon thinks that the neoplasm can be completely removed, extirpative surgery with curative intent should be considered as the frontline treatment. The few exceptions to this axiom are neoplasms that are highly sensitive to radiation (or chemotherapy) and if the cosmetic or functional values are judged to exceed the increased cost of radiotherapy. If the surgeon thinks that a clean surgical margin is not possible, an adjunct treatment with radiation should be considered. Radiation treatment is most effective as a treatment when the neoplastic cells are of smaller volume, well oxygenated, dividing rather than resting, and where surrounding normal cells in the margin can be sufficiently protected. The surgeon's role is to understand that large neoplasms have increased populations of resting, hypoxic, and dying cells that are resistant to irradiation, so cytoreductive surgery that removes the less susceptible cells is beneficial to successful irradiation of the remnant neoplasm. If this approach is taken, the goal is cytoreduction and a tension-free closure, with a flat, simple scar that will heal readily so that radiotherapy can be initiated as soon as possible.

RESPONSE OF NORMAL TISSUE TO RADIATION

Because radiation induces change in normal tissue, adversely affects wound healing, and complicates surgical procedures in previously operated tissues, it is important to begin with a brief review of the effects of radiation on normal tissue. More details are available in targeted reviews.[26–29] Cellular injury results from random ionizing events and random cell death. Ionization produces accumulation of intracellular free radicals that, with direct radiation injury, may induce critical disruption of DNA or organelles. With irreparable damage, cells typically die within 4 cell divisions.[30] Depending on the particular cell population, cell death may occur during mitosis, interphase, or subclinical apoptosis, and some cells may leave senescence through differentiation.

The science behind radiotherapy, radiobiology, is substantial and sophisticated. However, like surgery, clinical radiotherapy has also included much clinical trial and experience derived from individual patient variation. In addition, much of the science continues to be extrapolated from unfractionated (single, large) total doses,[31,32] whereas clinical radiation is usually administered in multiple fractions. The responses of normal tissues to irradiation are described in operational terms as acute, consequential, and late effects rather than more modern mechanistic terms that better describe the underlying cellular and molecular events.[33]

Acute radiation effects develop within hours to days of irradiation and are explained by injury to a population of cells undergoing rapid turnover. When acute responses become clinical, their significance is more related to the individual's response to tissue irradiation than to the dose. Clinical signs result from the loss of a sufficient number of cells or functional units such as when irradiated epithelium experiences normal exfoliative loss, failure of sufficient cellular replacement, and the consequences of bacterial invasion. Depending on the particular cell population, cell death may occur during mitosis, interphase, or subclinical apoptosis, and some cells may leave senescence through differentiation.

Clinical experience with tissue undergoing irradiation mandates that the tissues be examined daily. Irradiated tissues become progressively inflamed and less able to regenerate during the course of being irradiated. The response of the patient to inflammation is often self-mutilation and this must be prevented. Such behavior should be detected early and topical medicaments, antiinflammatory medication, and physical barriers should be applied to protect the tissue. Once wounded, irradiated tissue healing is slowed and remains suppressed while irradiation continues and for an interval thereafter. Because stem cells tend to be resistant to irradiation, they are the source of healing in irradiated tissues. The rate of healing depends on the supportive care provided to the tissues, the health of stem cells, and the native tissue turnover.

Late radiation effects develop months to years after irradiation. Late effects tend to occur in tissues with a slower rate of turnover, such as neural tissue, fat, muscle, liver, kidney, bone, and cells with slower turnover adjacent to rapidly dividing cells, such as the intestine. The mechanisms of late effect are not thoroughly explained, but are understood in terms of the cells as a microcommunity, interrelating through cytokines, chemokines, growth factors, and other signaling molecules, which is beyond the scope of this article. Of high significance to the surgeon is the role of the vascular endothelium. Vascular endothelium lies somewhere between rapidly dividing and slowly dividing cells. To a certain extent, the dose to all tissues is limited by the dose that might induce ischemia through vascular irradiation. Damage to vasculature causes leakage, fibrin deposition, collagen production, and fibrosis; however, it is more complex than vascular leakage with cellular responses such as mast cell chymase and matrix metalloproteinase-1 (MMP1).[34] Injury to the vasculature mimics other forms of wounding and the tissues respond in a similar manner with thrombosis, induction of inflammatory cytokines, growth factors, leukocyte migration, and endothelial budding and regeneration; however, the sequence of inflammation to fibrosis results in normal tissue loss or dysfunction. Some tissues may be partially rescued after radiation injury. Laboratory-manipulated human lipoaspirates (fat) infused into irradiated (single dose of 45 Gy) subcutaneous tissues of wild-type friend lukemia virus B (FVB) mice experienced a downregulation of transforming growth factor beta/SMAD gene famly member 3 (TGF-β/SMAD3) (profibrosis) response and decreased collagen production.[35] Placement of breast implants in human beings after mastectomy and radiation have been considered a surgery of higher risk for failure. Autografting of fat into the subcutis permitted successful alloplastic implant reconstruction.[36] Such microenvironmental

restructuring alteration is only one of many avenues being evaluated to modulate radiation injury. However, cytokine and growth factor–driven tissue repair might also provide harmful stimuli if neoplastic tissue remains in treated tissues.

Consequential late effects are acute reactions that fail to heal completely and persist into the late period. For instance, irradiated stem cells may be unable to differentiate fully because of constitutive or microenvironmental alterations.[37] Such primary lesions add to the overall damage.[38] There seems to be an increase in occurrence and risk for consequential late effects because of well-established syndromes like radiation recall, in which inflammation recurs in irradiated tissue when certain chemotherapeutic and other drugs are administered systemically.[39] Aggressive new combined treatment regimens, especially with antiangiogenic chemotherapeutics, small molecule therapy, and targeted therapy pose additional threat for consequential effects. As if the relationship of radiation and normal tissue were not complicated enough, the neoplasm and its satellites produce cellular mediators that can modify the local tissue environments and compromise normal tissue response or recovery. In addition, although uncommon in veterinary patients, radiation can induce oncogenesis.

SURGERY OF TISSUE TO BE IRRADIATED

Surgery interposed before or after tissue irradiation further increases the complexity of radiation treatment by introducing wounded tissue into the equation. Normal wound healing is a highly ordered sequence of vasocellular migration and proliferation events that are modulated by growth factors, cytokines, interleukins, proteinases, and other factors. Repetitive wound irradiation disrupts this progression resulting in repetitive inflammatory stimuli, cell injury, and imbalance of wound modulators even though irradiation promotes many of the same factors found in normal wound healing. The veterinary literature is numerically weak on the subject of healing of irradiated wounds.[24] One longitudinal clinical study showed that skin flaps prepared in 26 dogs that were subsequently irradiated experienced complication in 20 for which 6 required reoperation and 4 remained unresolved.[40] Flaps that were planned as a part of the initial tumor resection and reconstruction had a higher success rate than those designed to correct a problem or failure of radiotherapy.

There is an adage that states that tissue often heals in spite of the surgical technique. This adage is not true for most irradiated wounds. Besides inducing damage to the normalcy of tissue, radiation further delays healing by multiple mechanisms such as inducing endothelial apoptosis and reducing basic fibroblast growth factor (bFGF)[41] and MMP1.[42] Surgery for tissues that are to receive irradiation requires optimal operative attention that begins with the discussion between the surgeon and radiation oncologist as to the probable type of radiation treatment required. The depth and composition of the wound determine whether and which radiation treatments might be considered. The wound should be prepared to optimize the radiation oncologist's ability to treat. If the depth of tissue to be irradiated is greater than 3 cm (or if electrons are not available), photon radiotherapy is required and different surgical care is used. The optimum surgical wound for photon radiation results in a zone of injury well demarcated by judicious placement of steel or titanium vascular clips or skin staples[43] and a wound well supported by sutures. The most important consideration for the radiation oncologist is adequate targeting of the neoplastic wound remnant (bed) and a sufficient margin of surrounding tissue. After a surgical wound has been closed, the internal changes are impossible for the radiation oncologist to imagine. How deep? How much undermining? How much shifting of tissue

has taken place secondary to wound tension and closure? From the outside, the wound is the center of the lesion and although this view is refined for planning by intravenously contrasted, cross-sectional imaging, the surgeon can further assist by placing internal fiduciary markers (Fig. 1).

In body sites where full penetration by photon radiotherapy risks inducing lethal secondary effects, electron radiation is considered as an alternative treatment. Shallow electron fields are more demanding for the surgeon because, if not properly prepared, electron therapy may have to be abandoned because of probable failure. For best (uniform) dosimetry, the optimum surgical wound for electron radiation results in a wound bed of uniform thickness, flat surface, compact symmetry, absence of osseous or metallic obstructions, and is well supported with suture.

Wound geometry influences dosimetry and electron delivery. In flat, compact surgical wounds, electrons are easier to deliver because dose distribution loses uniformity if the wound differs in depth or if the body falls away over a curve. As particles, electrons are impeded by mass and the denser the mass the more rapid the dose reduction. Even soft tissue inhomogeneity can adversely influence dose distribution, but, more importantly, the presence of dense tissue, bone, or metallic implants can attenuate or block electrons and spare neoplastic cells. Electron radiation is not used in fields where neoplasm may be blocked by bone or implants. When appropriate, the surgeon should remove potentially obstructing bone and limit hemostatic methods to ligature and electrocoagulation, never metallic clips.

Conventional excision techniques result in wounds that are less compact than necessary. For example, most linear incisions must be approximately 1.5 times the length of a subcutaneous mass for adequate primary skin retraction and visualized excision. A linear excision that incorporates skin lengthens during closure because the curved edges are straightened. The length of these excisions can be reconfigured by using a curvilinear incision; usually of S shape (Fig. 2), which results in an incision of similar length for access, but that is more constrained for a rectangular field for irradiation.

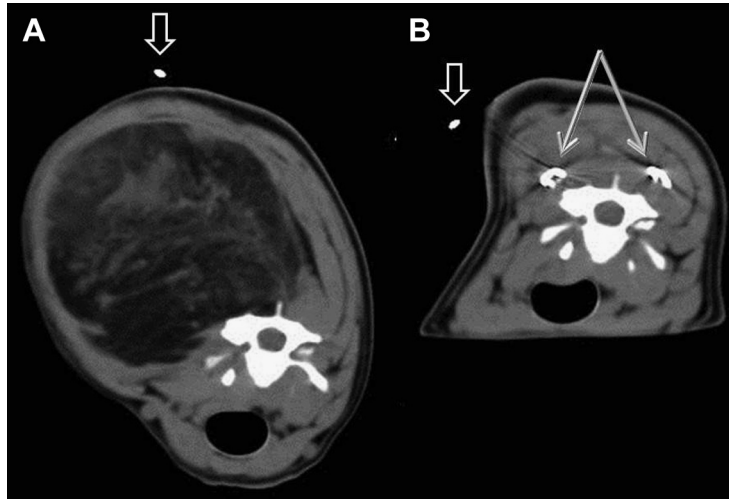

Fig. 1. Internal fiduciary marking of a liposarcoma after marginal excision. Preoperative (*A*) and postoperative (*B*) corresponding cervical spine CT images. Note the external fiduciary markers (*open arrows*) and internal staples (*thin arrows*) to assist the radiotherapist in treatment planning. Multiple staples were placed, particularly at the depth of the wound to assist planning to protect the cervical spinal cord.

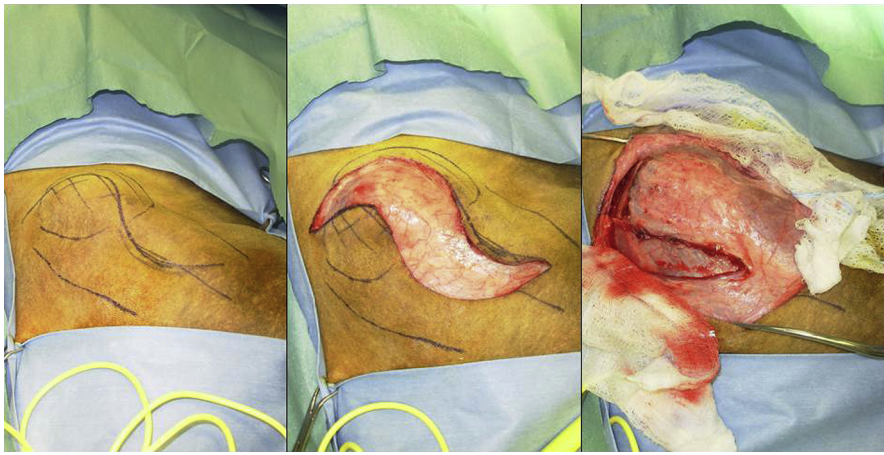

Fig. 2. Incision plan for partial scapulectomy with potential need of postoperative electron irradiation. Sketch of anatomic and disease structure overlain by S-shaped incision plan (*left*). S-curved incision (*middle*) permits reflection of flaps that improve access to the deeper structures (*right*). The plan achieves visualization with a compact wound. This closure does not extend over the dorsal body curvature and is absent angular flaps as with a T incision.

Wounds that are to receive radiation should be closed with the simplest tension-free technique. Wound tissue must be supported for longer than normal healing and remodeling periods so permanent or long-lasting monofilament sutures are recommended. The placement of drains is preferable to tissues separated by seroma. If a drain is placed, the egress sites must be able to be incorporated into the irradiated field. If drains are required for wound care, healing is delayed and radiation should also be delayed until tissue union is progressing. Anatomic layered closure including an intradermal layer is optimal. The skin may be sutured or stapled; however, if support of the wound throughout irradiation is desirable and wound closure will remain, a small gauge continuous suture will accommodate both photon and electron therapy.

Depending on the nature of the species, area wounded, tissues injured, and thoroughness of apposition on closure, radiation may commence immediately after surgery or be delayed. Cats seem to be more resistant to the acute effects of tissue irradiation than dogs. Simple wounds survive irradiation better than complexly reconstructed wounds. Well-apposed linear wounds in cats may begin to receive radiation as early as the same day of surgery. Nonlinear wounds are allowed to heal for 2 to 3 weeks before initiating irradiation. Although well-apposed linear wounds of dogs seem to heal satisfactorily, it is common to permit healing to continue for a minimum of 2 weeks before proceeding to irradiation. Wounds with complex angles and flaps are delayed for up to 4 weeks.

OPERATING IN IRRADIATED TISSUE

Operating in irradiated tissue is occasionally planned, but more often it is required to manage nonhealing ulcers and reoperation for recurrence of neoplasia. Useful veterinary reports are few. Retrospective studies occasionally remark on radiation toxicity, but less commonly relate surgery complicated by radiotherapy. In a retrospective study of nasal neoplasms receiving radiotherapy or radiotherapy followed by exenteration, the investigators concluded that radiotherapy may increase the risk of surgical complications. Dogs receiving radiotherapy followed by exenteration had increased

relative risk for nonhealing nasocutaneous fistula, osteomyelitis, osteonecrosis, and rhinitis, but they had a significantly longer survival time.[44]

Fibroplasia that occurs in irradiated tissue obliterates natural tissue planes and, surgically, the tissues are sticky, requiring sharp dissection or electrosection similar to removal of an inflamed lymph node or anal sac. Nerves are of similar texture to connective tissue and vessels are hidden so dissection in irradiated tissue is less precise and is accompanied by higher risks for injury to collateral near-field structures. When possible, surgery should be delayed until healing has progressed well into the remodeling period, beyond the natural production of elastin in the wounded area (usually beyond 1 month from healing), which results in the best possible tissue conditions. Preoperative planning for critical areas could be preceded by contrast imaging (magnetic resonance, CT, ultrasound). Surgery should be conducted with patience and finesse. The core surgical principles of dissection (primary wound retraction, accurate section, hemostasis, traction with countertraction, and avoidance of blind undercutting dissection) do not differ from those of conventional surgical oncology and reconstruction. The surgeon similarly cannot rely as much on the forgiveness of the healing processes in irradiated tissues. Even free vascularized tissue grafts have a higher complication rate when applied to irradiated tissue.[45] Free-graft survival is mostly unknown in veterinary medicine at present but was shown to be improved in a subsequent study by the topical application of vascular endothelial growth factor (VEGF).[46]

Should an entire irradiated tissue field be removed? Under most considerations, if complete surgical removal is possible, surgery should have already been performed as the frontline therapy. However, there are circumstances in which radiotherapy is elected by the clinician or owner rather than surgery as the frontline treatment, because of a likely successful response, and when presurgical radiation improves the probability of successful multimodal therapy. This strategy has been used for feline injection site sarcoma, with preoperative radiation followed by resection.[47] There is not a clear rule as to which approach is better in feline injection site sarcoma: preoperative radiation followed by surgery, or surgery followed by radiation.[48] Each case needs to be considered individually. However, the ability to achieve clean margins of resection seems to be the most significant factor in successful treatment of this disease.[11,47]

In instances in which radiation has been performed before surgery, such as failed nasal planum radiotherapy for squamous cell carcinoma, clinical experience has

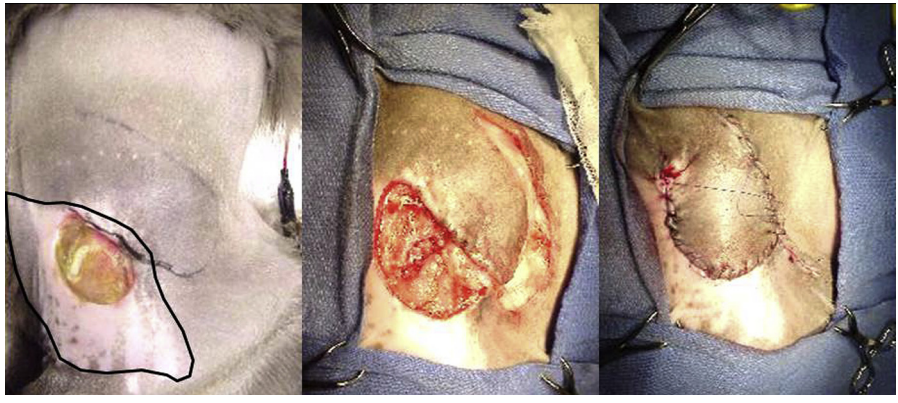

Fig. 3. Random rotation flap to repair radiation ulcer excision. Radiation site outlined (*left*). Excision of ulcer and flap prepared from adjacent nonirradiated tissue (*center*). Completed flap with minimal rotation torque of base and tension-free closure (*right*).

resulted in successful excision and healing. When addressing reoperation of irradiated tissue, the practical steps to consider should therefore include the aforementioned core principles and tissue flaps introduced from adjacent tissues with less radiation-induced fibrosis (**Fig. 3**). Because tissue vascularity may be compromised, tension should be minimized, flap bases emboldened, and rotation lessened. When using advancement of V-shaped tissues a rounded V tip is more likely to survive, but clinical experience suggests that complex, multi-incision wounds are at higher risk.

SUMMARY

Surgery is a critical component in the treatment of most solid tumors in small animals. Surgery is increasingly being combined with adjuvant therapies such as chemotherapy and radiation and therefore surgeons who are treating cancer must have a good understanding of surgical oncology principles, cancer biology, and the roles and potential positive and negative interactions of surgery, radiation, and chemotherapy. The sequencing plan for these modalities should be determined before any form of treatment is initiated. The first task of the surgeon is to achieve a histologic diagnosis through incisional biopsy and to stage the patient. This information can then be used to develop an integrated plan for therapy that takes into account the treatment goals as well as the best modalities for achieving local and distant disease control. Local control involves surgery and/or radiation and control of systemic spread involves adjuvant chemotherapy. During surgical resection with curative intent, surgical oncology principles must be applied to ensure complete en bloc resection of the tumor without contamination of the tumor bed.

The surgical oncologist must have a working knowledge of the chemotherapy agents with which their patients are being treated and the effect that these treatments have on both the ability of tissues to heal and the effect on the blood cell counts, especially at the nadir. In general, an interval of 2 weeks should be allowed between surgery and chemotherapy or vice versa to avoid a negative interaction of these modalities. If this is not possible, particular attention should be paid to the patient's white blood cell and platelet count and care should be taken to allow for potential delayed healing. It is also important that the surgeon is aware of the considerations of operating in tissues before and after irradiation. Considerations that the surgeon should make if a mass is being resected marginally, with a plan to follow with adjuvant radiation, include the placement of metallic fiduciary markers at the internal limits of the surgical wound. Planning for electron radiotherapy is assisted if the surgeon composes a flat, compact wound of uniform thickness that contains no bone or metal that would block electrons. Wounds to be irradiated should be apposed by layers, tension free, and sutured with nonabsorbable or slowly absorbable suture. Simple, well-apposed wounds may be irradiated immediately, but wounds that are under tension, that required drains, or that required complex reconstruction should be rested until near the end of the proliferation phase of wound healing (beyond week 3). Radiation causes fibrosis in normal tissues, obliterating normal fascial separations. Surgery of irradiated tissue is hazardous because dissection must be sharp, vascular and neural structure is obscured, and vascular support for healing is already compromised. A good working knowledge of the surgical management of tumors with and without the addition of neoadjuvant or adjuvant therapies is essential to successful multimodal therapy for cancer in small animals.

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