

**Everything You Need to Know About Small Animal Clinical Oncology in 4 Hours**  
**Lecture 4: The Better Part of Valor – Making Rational Treatment Decisions for Veterinary Cancer Patients**

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**Introduction**

Coming to an understanding of the pet owner's goals and expectations from therapy is the first essential step in developing a sound treatment plan for the small animal cancer patient. Fundamentally, there are only three beneficial outcomes that can follow from cancer treatment: 1.) Cure; 2.) Extension of life in the absence of cure; or 3.) Improved quality of life in the absence of cure or extension of life. A clear recounting of whether any of these goals is achievable from a given course of therapy usually helps owners to make realistic decisions about their pets' medical care. However, such clarity can only be offered by veterinarians who understand the indications for and limitations of surgery, radiation therapy, and chemotherapy in the treatment of cancer. An encyclopedic knowledge of all possible permutations and applications of these therapies is not necessary to cultivating such an understanding – judicious attention to some basic principles will suffice. Adherence to these principles will help to avoid the two most detrimental outcomes of ill-considered cancer treatment: 1.) Failing to meet the expectations of the pet owner; and 2.) Inflicting harm on the patient without the prospect of benefit. So, for veterinarians to thoughtfully recommend surgery, radiation therapy, or chemotherapy for a small animal cancer patient, they must have a clear understanding of what these therapies can – and cannot – accomplish, as well as how they can potentially harm patients.

**Surgery, Radiation Therapy, and Chemotherapy for Cancer – How Can They Help?**

Surgical removal is usually the best initial treatment for localized cancers. It is also the only therapy with any significant chance to cure patients with cancer.<sup>1</sup> Because malignant tumors grow by invasion into surrounding tissues, curative-intent excisions must include a margin of grossly normal tissue around the tumor. For superficial tumors, this margin typically includes 2-3 cm of tissue in every lateral direction, and 1 fascial plane deep to the tumor. For deeply seated or visceral tumors, appropriate surgical margins are usually dictated by the need to preserve critical nearby anatomic structures, although achieving margins of similar extent is still a goal in these circumstances. When deciding upon the appropriate fascial plane to resect deep to or around a tumor, veterinarians must consider that bone, cartilage, tendons, fascia, and other dense fibrous connective tissues are more robust barriers to cancer invasion than fat, subcutaneous tissue, or muscle.<sup>2</sup> Resecting portions of these dense connective tissues along the deep surgical margin is essential to curative-intent excisions. Furthermore, the extent of margins needed for surgical cure can depend very much upon the tumor type. For example, a 2-3 cm surgical margin frequently is insufficient to cure feline injection site sarcomas, which have a propensity for extensive local invasion. It has been suggested that a surgical margin of 5 cm laterally and 2 fascial planes deep to the tumor is necessary for a reasonable expectation for surgical cure of these tumors.<sup>3</sup>

Radiation therapy, like surgery, is generally reserved for localized cancers. One of the most common indications for radiation therapy is as adjuvant treatment marginally (incompletely) excised cancers. In this scenario, microscopic residual cancer surrounding the surgical scar is the target for radiation. This application of radiation therapy is frequently employed in dogs with incompletely excised soft tissue sarcomas or cutaneous/subcutaneous mast cell tumors that are of low-to-intermediate histopathologic grade.<sup>4,5</sup> In these settings, the use of radiation therapy typically is associated with long-term disease-free survival, which is likely tantamount to cure. In contrast, radiation therapy is rarely curative for macroscopic cancer. However, pain and loss of function associated with nearly any

macroscopic cancer can be palliated with radiation, which frequently improves quality of life for several months.<sup>6</sup> In some cases, more durable palliation of macroscopic cancer can be achieved when treating anatomically inaccessible tumors, such as nasal tumors and intracranial tumors, with more aggressive treatment regimens. Careful patient selection is critical to the successful use of these more aggressive regimens. They are generally most appropriate for patients with relatively low-stage tumors and limited tumor-associated morbidity. Use of these more aggressive protocols in patients with advanced-stage disease frequently results in greater treatment-related morbidity without concomitantly improving survival.

Unlike surgery or radiation therapy, chemotherapy is useful for the treatment of both locally advanced and metastatic cancers. One of the primary indications for chemotherapy is to treat macroscopic chemoresponsive tumors that are not good candidates for surgical resection or irradiation. The term “chemoresponsive” is not defined clearly in the veterinary literature, but the author generally reserves it for tumors that have a greater than 1 in 3 chance of reducing in size by at least 50% following drug treatment. Almost without exception, the only tumors that meet this definition are hematopoietic (“round cell”) tumors, such as lymphomas, mast cell tumors, and plasma cell tumors. Other tumors that have a reasonable chance to shrink following chemotherapy are squamous cell carcinoma and urothelial (transitional cell) carcinoma.<sup>7,8</sup> Most other macroscopic cancers are quite unlikely to reduce in size following chemotherapy. A second major indication for chemotherapy is as an adjuvant to surgery and/or radiation therapy to treat microscopic metastatic disease. The intent here is to extend survival relative to what is achievable with local therapy alone in patients with highly metastatic cancers. To the author’s knowledge, chemotherapy has not been proven (in a randomized, controlled clinical trial) to extend survival in this setting for any veterinary cancer. However, there is convincing evidence that chemotherapy probably extends survival for dogs with appendicular skeletal osteosarcoma<sup>9</sup> and splenic hemangiosarcoma<sup>10</sup> in this setting.

From the preceding discussion, it should be inferred that two essential prerequisites to the informed use of surgery, radiation therapy, and chemotherapy are: 1.) an accurate histopathologic diagnosis of cancer, and 2.) complete tumor staging information. Histopathologic grade and/or tumor stage are of significant prognostic relevance to the vast majority of small animal cancers. Therefore, these variables are major determinants of the benefit that can be expected from a given course of therapy. Aggressive, curative-intent therapy is most appropriate for low-stage, low-grade cancers. High-stage and/or high-grade cancers, on the other hand, are unlikely to be curable with any therapy or combination of therapies, and may therefore be better treated with palliative intent.

### **Surgery, Radiation Therapy, and Chemotherapy for Cancer – How Can They Do Harm?**

All medical interventions, no matter how seemingly innocuous, can have side effects. Nowhere is this truer than in the arena of cancer therapy, in which some degree of short-term treatment-related morbidity is virtually assured, regardless of the specific treatment used. Cancer surgery, radiation therapy, and chemotherapy therefore must be utilized with an eye towards balancing treatment-related morbidity with therapeutic benefit. It is critical that owners pondering a course of cancer-directed therapy for their pet be provided with a frank summary of the possible side effects of that therapy. Many individuals are willing to accept their pets experiencing some level of treatment-related morbidity if there is a rational expectation for a significant benefit from treatment. Encouraging pet owners to pursue aggressive therapy in these scenarios is reasonable. However, when the therapeutic calculus shifts to favor treatment-related side effects over therapeutic benefit, pet owners should be steered towards less aggressive options.

A general understanding of the nature of the morbidity induced by various cancer therapies will help veterinarians to make rational recommendations to pet owners about when to choose these therapies. The relative morbidity associated with aggressive cancer surgeries often exceeds that associated with surgical procedures typically performed in a general practice setting. Wound dehiscence, bleeding, infection, and acute pain all are potential complications of curative-intent cancer surgery.

Apprehension associated with these complications should not compel veterinarians to perform less aggressive tumor resections. Such action often increases the likelihood of local tumor recurrence, largely sacrificing any prospect for surgical cure. Rather, if a clinician is unfamiliar or uncomfortable with the techniques needed to effect surgical cure for a specific cancer, a more experienced practitioner should be consulted, or an alternative therapy to surgery should be considered.

Curative-intent radiation therapy (also termed *definitive radiation therapy*) inevitably results in acute side effects to tissues with a high rate of cellular turnover, such as skin and mucosa. Moist desquamation of these tissues (so-called "radiation burn") typically becomes apparent towards the end of a course of definitive radiation therapy, then progresses for a period of about 1-2 weeks following completion of therapy. Tissues undergoing moist desquamation are painful and pruritic, though supportive care often is helpful at ameliorating these unpleasant side effects. It is important to prepare owners to expect these side effects, while helping them to understand that they are only temporary. Most acute side effects have resolved entirely within 4 weeks of completing a course of definitive radiation therapy. Some clinicians may be tempted to use alternative radiation therapy dosing protocols in the curative-intent setting in order to minimize acute side effects. These protocols involve fewer radiation treatments, larger radiation doses per treatment, and a lower total dose of radiation. While such protocols do produce fewer acute side effects, they offer a lower potential for cure because of the lower total radiation dose. They also may be associated with a greater risk for irreversible late side effects, such as tissue fibrosis or necrosis. These protocols typically are reserved for palliative-intent therapy.

Chemotherapy, whether used to treat macroscopic or microscopic cancer, can rarely be given with true curative intent to veterinary patients. However, if administered judiciously, chemotherapy does have the potential to extend life for patients with several cancer types. To achieve this, however, chemotherapy must be given at the *maximally tolerated dose*, which results in predictable, dose-dependent side effects. The most common side effects of chemotherapy are neutropenia due to bone marrow injury and gastrointestinal signs (vomiting, diarrhea, inappetence) due to injury to the gastrointestinal epithelium. As with acute side effects of radiation therapy, these chemotherapy-related side effects are reversible. Furthermore, they are only life-threatening in approximately 5-10% of treated patients. However, as with other therapies, the likelihood of these serious side effects must be balanced against the likelihood of treatment-related benefit. In some cancer patients, this likelihood of benefit from chemotherapy is probably far less than even this nominal 5-10% threshold.

### **Limitations of Surgery, Radiation Therapy, and Chemotherapy in the Treatment of Cancer**

As mentioned previously, the histologic cancer type, histopathologic grade, and tumor stage are major determinants of the most appropriate cancer therapy for a given patient. This is because these are the tumor characteristics that impose the greatest limitations on the benefit that can be derived from cancer therapy. Cancer type is strongly associated with sensitivity to radiation therapy and chemotherapy. For example, hematopoietic tumors, such as lymphomas, mast cell tumors, and plasma cell neoplasms are frequently sensitive to both radiation therapy and chemotherapy, with even macroscopic tumors often shrinking rapidly in the face of such treatment. This likely results from a tendency of the cells from which these cancers were derived to undergo apoptosis in the setting of even relatively minor genomic injury.<sup>11,12</sup> Most carcinomas and sarcomas, on the other hand, are unlikely to respond to chemotherapy or radiotherapy in the macroscopic disease setting. Attempting to use these therapies with curative intent in patients with these tumors therefore is ill-advised.

Cancer grade further determines the likelihood that treatment will benefit a patient. High-grade tumors, on the whole, are more locally invasive and more likely to metastasize than low-grade tumors. As a result, surgical cure of most such tumors is impossible. The author questions whether surgical intervention for many high-grade tumors is even of palliative benefit in many cases, as local recurrence may develop rapidly following marginal excision of these tumors. Recurrent tumors frequently are more biologically aggressive and anatomically widespread than primary tumors, which can make them sources

of profound morbidity to patients. The rapid growth rate of high-grade tumors does allow them to respond temporarily to chemotherapy and radiotherapy in many cases. However, these tumors also frequently harbor driver mutations that make subpopulations of cells within the cancer inherently resistant to chemotherapy and radiotherapy. This phenomenon may extend even to the treatment of these cancers in the adjuvant (microscopic disease) setting. Therefore, treatment of high-grade cancers should be considered carefully, often with an eye towards palliating disease-related morbidity while limiting side effects of treatment to the greatest possible extent.

Tumor stage is the final major factor that limits the benefit that can be conferred by cancer treatment. The stage refers to the size of the primary tumor, as well as whether or not it has seeded macroscopic metastatic lesions. Surgery and radiation have little role in the treatment of metastatic cancer lesions. Even chemotherapy often confers limited benefit when treating macroscopic metastatic disease. This is because larger tumors are inherently more difficult to control with chemotherapy, as the cell-killing potential of chemotherapy is inversely proportional to the number of cells in a tumor.<sup>13</sup> The same is true of radiation therapy.<sup>14</sup> As a result, the doses of chemotherapy and radiation needed to eradicate large tumors would result in death or permanent dysfunction of the patient. Surgery, on the other hand, does have some potential to cure large tumors, but only if they are low-grade and non-metastatic. Because curative-intent surgical resection of large tumors inevitably results in significant short-term morbidity, the decision to pursue such therapy must be informed by tumor grade and stage. Therefore, collecting this information by incisional tumor biopsy followed by careful clinical staging is imperative before planning aggressive resection of large tumors. Aggressive resection in the setting of metastatic disease or a high-grade tumor is unlikely to extend survival, and may very well result in greater morbidity than that inflicted by the tumor itself.

### **Summary**

The deleterious consequences of therapy must be weighed carefully against the prospect for benefit when considering treatment options for cancer patients. Aggressive therapy does have the potential to cure some patients with cancer, but always results in some degree of short-term morbidity. Veterinarians must understand the features of a cancer that favor or oppose a beneficial outcome from aggressive therapy. When the odds of serious treatment-related morbidity outweigh those for significant benefit from therapy, a palliative approach should be taken. While this palliative approach may include surgery, radiation therapy, or chemotherapy, the application of these therapies with discretion is critical to assuring that treatment benefits rather than harms patients. It is the author's firm belief that paying careful attention to the principles of cancer treatment summarized here will help veterinarians to cultivate this sense of discretion, ultimately enabling them to develop treatment plans that benefit the vast majority of small animal cancer patients.

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