Principles and Applications of Radiation Therapy

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Radiation therapy is emerging as a beneficial and increasingly accessible treatment option for companion animals with cancer. Various types of radiation are available with different properties that may make one more suitable than another for treating a specific tumor type. Radiation therapy can be used as the sole treatment or as part of a multimodality treatment course to result in local or locoregional tumor control, or as palliative therapy for pain control. When radiation is a potential treatment option, it should be considered early in the decision-making process to ensure that the appropriate diagnostics and other treatment modalities are considered to provide the best potential outcome. This article is intended to provide an overview of the types of radiation therapy that are available, the indications, and the potential acute and late radiation side effects.

In the past, radiation therapy (RT) has played a relatively minor role in the care of companion animals with cancer. Until relatively recently, there have been only a limited number of veterinary RT facilities. In addition, information available for veterinarians and pet owners about the utility of RT for treating common tumor types was based on information from small case series. In recent years, there has been a dramatic increase in the availability of RT and in information about its effectiveness in the treatment of a number of different tumor types. Pet owners and veterinarians have become proactive in seeking more advanced treatment modalities for pets with cancer. There have also been a number of technological advances in radiation delivery that have increased the potential benefits of radiation while minimizing the risks associated with treatment. All of these changes have contributed to an increased demand and a greater role for RT as a treatment option in veterinary cancer patients.

To maximize the utility of RT, it is important to have an understanding of the different types of radiation that are available and their potential benefits and limitations. If RT is to be a part of an animal's cancer treatment, then it is best to consider this possibility early in the diagnostic evaluation. This allows for planning of the appropriate diagnostic tests, surgery, chemotherapy, or other treatments. A coordinated approach to cancer management will facilitate the optimization of therapy, with the potential for increased disease-free interval and survival.

It is important to have an understanding of the indications for RT. RT can be used to treat a wide variety of tumor types. Some tumors are best treated using RT as the sole means of treatment, whereas with other tumor types, it is best to combine RT with either surgery and/or chemotherapy to achieve the best results. These indications are not only dependent on the tumor type but also on many other factors that can vary between patients. The variables to consider when deciding whether or not a patient is a good candidate for RT include the histopathologic tumor grade, clinical stage, tumor location, and the overall health status of the patient. Finally, radiation can lead to side effects that commonly start during the latter part of RT and progress after the completion of therapy before resolving. RT protocols will result in some side effects in all patients. Therefore, it is important to be able to identify RT side effects and manage them in a way that will result in a minimal amount of discomfort and a rapid return to normal.

Types of RT

The following discussion will provide a brief overview of the different types of RT that are commonly used for treating animals with cancer, and the properties of these different modalities that might make one better suited for treatment of a specific patient. The two RT modalities that are used most commonly in veterinary oncology are brachytherapy and teletherapy. Brachytherapy (brachy, meaning 'short') involves using radioactive sources that give off radiation, as the source decays, with a limited distance of penetration, such as iridium-192. In brachytherapy, the radiation source is placed on or within the tumor. The primary benefit of brachytherapy is that a higher dose of radiation can be delivered preferentially to the local tissues while avoiding delivery of a significant radiation dose to surrounding normal tissues. Interstitial brachytherapy, or placement of temporary or permanent radioactive sources within the tumor itself, is one method of brachytherapy. This treatment involves using high-energy radioactive sources that pose a radiation safety hazard to people who work with them, or in the case of permanent implants, to anyone that comes into contact with the patient. These safety hazards and radiation regulations have made interstitial implants more difficult to work with, and have limited their availability and use in veterinary oncology.

Another type of RT, known as plesiotherapy (plesio, meaning 'close' or 'near') utilizes a small-diameter probe (eg, 0.87-mm active diameter) of strontium-90, which gives off low-energy beta radiation. The limited penetration of beta radiation makes this type of therapy very useful for treatment of superficial tumors, particularly where surgery might be difficult, eg, eyelid tumors. Strontium-90 has shown to be useful, particularly in the treatment of superficial tumors that occur in multiple sites, such as solar-induced dermal squamous cell carcinoma in cats. However, due to the limited availability and indications for brachytherapy in animal patients, these treatment modalities will not be discussed further. Teletherapy

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(tele, meaning 'distance'), ie, external beam RT is the most commonly used RT modality in animals with cancer and is the focus of the following review.

External beam RT involves delivery of radiation from a source that is located at a distance from the patient. In most situations, the beam that is produced is made up of photons or packets of energy that act like a beam of light in that they have properties like both waves and particles. In external beam RT, photons can be produced of different energies, which determine the properties of the radiation and how it will interact with the patient. Different RT machines produce a wide range of energies but, based on the energy level, they are divided into either orthovoltage or megavoltage (high-energy) radiation units.

Orthovoltage radiation is produced using the same principles that are used to create a beam of radiation in a diagnostic x-ray unit. The energy of the beam produced is typically in the range of 150 to 500 kVp. When this type of beam interacts with a patient, the maximum deposition of radiation dose is in the skin, with the dose falling off rapidly as the beam penetrates into the deeper tissues. Orthovoltage RT also results in the deposition of a greater dose in tissues with a high atomic number (ie, Z) such as bone. Orthovoltage RT is most appropriately used for the treatment of superficial tumors. The deposition of the maximum dose at the skin surface results in increased skin reactions in the radiation field with orthovoltage radiation, whereas the increased deposition of dose in bone in the irradiated field has the potential to cause increased bone damage. Over the years, megavoltage radiation units, including cobalt 60 and linear accelerators (LINAC), have to a large extent replaced orthovoltage radiation units as the most common type of teletherapy units at veterinary radiation facilities.

Megavoltage radiation involves the use of photons with energy of greater than 1 MV (million volts). The higher energy radiation beam penetrates further in tissue, allowing for treatment of more deep-seated tumors. With megavoltage RT units, the maximum dose is not deposited until some depth below the surface, resulting in a skin-sparing effect (Table 1). Megavoltage RT units include cobalt 60 and linear accelerators. The main difference between cobalt 60 teletherapy units and linear accelerators is how the radiation is produced. Cobalt machines involve the use of a radioactive source that gives off radiation as the source decays. An approximately 2-cm piece of cobalt 60 is housed within the head of the machine and is moved to the on position over the radiation treatment field when the beam is on. This radioactive source decays over time, necessitating replacement of the source approximately every 5 years. Linear accelerators follow the same principle for producing radiation as diagnostic x-ray machines and orthovoltage machines, but are more complex pieces of equipment that produce radiation at higher energies. For both orthovoltage units and linear accelerators, the primary principle involved is that electrons are accelerated into a metal target, eg, tungsten, resulting in the production of an x-ray beam. One major benefit of higher energy LINACs (typically 6 MV and higher) is that they are also configured to produce a range of different energy electron beams. For example, a 6 MV LINAC can have 6 different electron beam energies that range from 5 to 14 MeV (million electron volts). Electrons are used to treat more superficially located tumors that may be overlying critical normal tissues, as the dose falls off rapidly with depth in the tissue (Table 1). The specific electron energy that is selected is based on the location of the tumor and the desired depth of penetration. Electrons are frequently used to treat patients postoperatively when there is relatively superficial, residual microscopic disease associated with a surgical scar.

TABLE 1. Approximate Percent Depth Dose Distributions for Different Types of Radiation Therapy

Type of RT	Energy	Depth of Maximum Dose (cm)	Depth of 50% of Maximum Dose (cm)	Depth of 25% of Maximum Dose (cm)
Orthovoltage	280 kVp	Surface	7.5	11.8
Cobalt 60	1.25 MV	0.5	11.6	21
LINAC (photons)	4 MV	1.0	14	25
	6 MV	1.5	15.6	28
LINAC (electrons)	5 MeV	1.0	2	2.4
	8 MeV	1.5	3.2	3.6
	12 MeV	2	4.7	5.3

External beam RT units all produce a beam of radiation that can be shaped and directed at the tumor. However, the beam often must penetrate through normal tissues to reach the tumor, resulting in side effects in the surrounding normal tissues. Delivery of excessive dose to overlying or surrounding normal tissues, and the potential for increased normal tissue side effects can potentially be minimized by using multiple beams with different beam-shaping devices and techniques that focus the delivery of radiation to the tumor while minimizing the amount of radiation delivered to the normal tissues. The unit of dose that is used is the Gray (Gy), defined as 1 J/kg, and is the energy deposited in the tissue. Another commonly used unit is the rad, equal to 1/100 Gy or 1 cGy.

Availability of RT

There are over 40 veterinary radiation facilities in the United States. Information about some of these sites and how to contact them for treatment information has been recently published.[1] However, new sites are continually being added to the list and, for the most up-to-date information, it is important to contact regional veterinary academic institutions and/or veterinary oncology specialty practices to locate the closest operational facility.

Indications and Course of Treatment

Palliative RT

Depending on the goal of RT, the intent of the treatment course can be described as either palliative or definitive. The goal of palliative RT (PTRT) is not to control the tumor or prolong survival, but rather to provide relief of a specific symptom (eg, reduction in the size of a mass that is causing obstruction, decrease in pain associated with a bone tumor) while resulting in minimal, if any, adverse radiation effects. This can be accomplished by delivering a small number of treatments, referred to as fractions, with a larger dose of radiation for each fraction. PTRT is recommended for patients with tumors that would not be expected to respond favorably to a more definitive course of treatment, or for a patient that presents with advanced metastatic disease but is symptomatic for the local tumor. At veterinary radiation facilities, upwards of 50% of patients that are irradiated are treated with PTRT due to the presence of advanced disease at the time of initial presentation. The most common indication is for patients that are experiencing pain as a direct result of the tumor.

PTRT has been used most commonly for pain relief in patients with appendicular osteosarcoma that are not considered surgical candidates, or if an owner has declined definitive therapy, such as combination amputation and chemotherapy. Treatment of osteosarcoma in these patients can result in pain relief, with a typical onset of some level of pain relief within 7 to 14 days after the first dose of radiation, and lasts on average for approximately 2 to 3 months.[2-4] PTRT was also evaluated for response in patients with a variety of tumors, including osteosarcomas and melanomas. This study showed a similar pattern of overall response.[5]

PTRT can also be used to try to alleviate obstruction of a vital passageway, for example, the upper airway. In this situation, if the tumor is one that can be expected to respond well to RT by decreasing in size, then treatment may lead to an improved quality of life, but is not anticipated to prolong survival.

There are a number of reports on the use and utility of PTRT for melanomas. Cells from human melanomas have been shown to be resistant to conventional doses of RT, possibly due to an increased ability of these cells to repair radiation damage.[6-8] This has lead some authors to recommend coarsely fractionated radiation to treat oral melanomas in dogs. Two studies have shown that oral melanoma in dogs can be treated with overall response rates of greater than 80% using either three or four radiation treatments with large doses per treatment (eg, 8 Gy/fraction). This results in long-term control of the local tumor in most dogs, but metastasis is still a major concern for oral melanoma and often is the cause of death.[9,10]

Definitive RT

Definitive full course RT is commonly used and has many indications in veterinary oncology. Full course RT is typically delivered in 12 to 21 individual treatments using a lower dose of radiation (eg, 3 Gy/fraction) for each treatment compared with PTRT, but a higher total dose (eg, 48 to 63 Gy). The actual number of treatments and the dose per treatment can vary depending on the species, tumor type, tumor location, and variations between radiation protocols that are used at different facilities as well as other factors. Full course definitive RT with a lower dose per fraction and a higher total dose provides the best chance for long-term local tumor control while minimizing the risk of significant late radiation side effects, which are more likely to occur with a more coarsely fractionated RT treatment protocol. In designing radiation protocols, the risks and difficulties associated with daily anesthesia over a prolonged time period are taken into account. Definitive RT can be used alone or in conjunction with other treatment modalities including surgery, chemotherapy, and supportive treatment for animals with cancer. The decision to use RT alone or in combination with other treatment modalities is dependent on the species, tumor stage, expected biologic behavior of the tumor, and other factors.

Common Tumor Types Treated with Radiation

Single Modality RT

Brain tumors are often treated with RT alone, particularly tumors that are difficult to approach surgically. Recent advances in imaging of brain tumors using computed tomography and magnetic resonance imaging have led to an increased ability to diagnose brain tumors,[11,12] as well as an improvement in the accuracy of delivery of radiation to the site of the tumor through the use of computed tomography-based, computer-generated RT planning. Studies have shown that RT is beneficial for dogs with brain tumors, resulting in survival times of up to 1 year with radiation alone.[13-16] This is in contrast to survival times of less than 2 months seen with symptomatic therapy alone.[14,17] Recent studies also suggest that RT may be of benefit as adjuvant therapy in dogs with brain tumors, specifically meningiomas, that are incompletely resected.[18,19] Dogs with pituitary macroadenomas may benefit from RT, and RT for these tumors has been shown to result in long-term tumor control.[20,21] Some studies of RT for brain tumors indicate that dogs with less severe neurologic signs have a better prognosis in terms of response to therapy and long-term survival.[14,20]

In cats, the most common primary brain tumor is meningioma and surgery alone often leads to long-term tumor control.[22,23] Therefore, RT plays less of a role in the primary treatment of feline brain tumors, but may be useful for postoperative treatment of cats with incompletely resected tumors.

There is a relatively large body of literature available on the utility of RT alone or in combination with surgery or chemotherapy for the treatment of nasal tumors in companion animals. Nasal tumors in dogs and cats have been treated most commonly with RT alone. The exception to this is that with lower energy orthovoltage RT, a rhinotomy and cytoreductive surgery is recommended before irradiation, due to the poor penetration of radiation to the full depth of the nasal cavity.[24] Megavoltage RT using a cobalt machine or a linear accelerator results in good responses, and in these situations, prior surgery has not improved the likelihood of tumor control or increased overall survival.[25] With either of these two treatment scenarios, the median survival times for dogs treated with RT has ranged from 8 to 14 months.[24-27] There is a tendency for dogs with nasal sarcomas to do better than carcinomas and for dogs with nasal adenocarcinomas to do better than other types of carcinomas (eg, undifferentiated carcinomas and squamous cell carcinomas).[24,25] There have not been as many reports on the treatment of cats with nasal tumors. However, the responses, tumor control, and survival times are equivalent or better than what has been reported in dogs.[28,29] In particular, nasal lymphoma, if localized to the nasal cavity, can have an excellent chance for long-term local tumor control with radiation alone, although some cats will fail systemically.[29]

The majority of oral tumors are treated most effectively using surgical excision, requiring a mandibulectomy or maxillectomy. However, in select instances, RT may be indicated as the primary therapy or as an adjunct to surgery. As discussed above, PTRT or coarse fractionation is useful in the treatment of oral melanomas, although it does not impact the development of metastatic disease. In oral squamous cell carcinomas and fibrosarcomas, local recurrence is a greater concern than metastasis, and these tumor types may be controlled locally for a significant period of time with radiation alone.[30] Periodontal tumors, such as acanthomatous epulides, are effectively controlled by surgical resection. However, at times it may be difficult to completely resect an acanthomatous epulis, or an owner may decline surgery, and a good response can be obtained by RT alone. RT for acanthomatous epulis typically results in an excellent chance for a complete response and long-term control of the tumor.[31] The most common oral tumor in cats is squamous cell carcinoma. This tumor usually carries with it a very poor prognosis due to aggressive invasion and destruction of the surrounding bone and soft tissues. Therefore, PTRT is usually indicated for pain management in addition to other palliative measures. RT can be used successfully in conjunction with an aggressive surgical procedure for mandibular squamous cell carcinoma in cats with good results, but it does require that the tumor be surgically resectable.

Adjuvant RT

Probably the most widespread and effective use of RT in veterinary medicine is the use of RT in conjunction with surgery for long-term local tumor control. This includes adjuvant treatment of cutaneous mast cell tumors in dogs, and soft-tissue sarcomas in dogs and cats, including vaccine-associated sarcomas in cats. The principle behind adjuvant therapy is that surgery is used to remove the bulky disease and radiation plays the role of killing or sterilizing tumor cells that are left behind or would be left behind by surgery.[32] In a number of different tumor types, the combination of these two modalities has been found to be an excellent way to prevent local recurrence of tumors that would be expected to recur following use of either modality alone.

Mast cell tumors in dogs are often difficult to completely resect due to the size of the primary mass at presentation, microscopic extension of tumor into the surrounding tissues, or the location of the primary tumor that prevents wide excision (eg, on an extremity). Often, histopathologic margins reveal an incomplete resection with presumed residual microscopic disease at the surgery site. Mast cell tumors with an intermediate histologic grade (ie, grade II) could be expected to recur in this situation, but are not likely to metastasize. In this situation, RT has been shown to result in excellent long-term control in greater than 90% of cases.[33-36] High-grade (ie, grade III) mast cell tumors may also be treated with adjuvant RT. However, the benefit of using local therapy in this setting may be limited by the increased metastatic rate seen with high-grade tumors.

Soft-tissue sarcomas in dogs often present the surgeon with the same difficulties as encountered with mast cell tumors. Traditionally, soft-tissue sarcomas have been considered to be poorly responsive to RT, based on the poor local control seen in studies of dogs that had gross disease at the time of irradiation.[37] In recent years, two studies have been published that indicate that treatment of incompletely resected soft-tissue sarcomas with postoperative RT results in long-term local control of the tumor in greater than 75% of the cases.[38,39] Both of these tumor types in dogs—mast cell tumors and soft-tissue sarcomas—can therefore be managed by surgery first, followed by RT, if indicated based on assessment of the surgical margins on histopathology.

The treatment of cats with vaccine-associated sarcomas (VAS) is typically more involved and often requires more extensive and careful planning before the initiation of treatment. As opposed to soft-tissue sarcomas in dogs, the extensive local invasion of VAS into surrounding tissues in cats commonly results in recurrence, even after extensive surgery and regardless of the histopathologic margins.[19] Therefore, it seems likely that aggressive multimodality therapy is the best treatment option. Because of the difficulties in treating VAS, there has been a great deal of interest in determining whether preoperative or postoperative RT is the best way to approach these tumors. The potential benefits of preoperative radiation include smaller radiation fields that include less normal surrounding tissues, and the ability to treat the tumor cells earlier on in the course of treatment. Also, tumor cells that are located in a healed incision may be hypoxic, which will result in those cells being 2 to 3 times more resistant to the effects of radiation in the postoperative setting.

Early reports on the response of VAS to surgical treatment alone revealed frequent recurrence and difficulty in obtaining local control.[40,41] Recent studies have shown that the use of RT in addition to surgery can potentially double the duration of local control.[42,43] Additional studies investigating the use of preoperative RT with chemotherapy revealed similar results.[44,45] Future studies are needed to determine the exact role of chemotherapy in the treatment of VAS in cats.

One concept that should be kept in mind when exploring the different indications for RT is that it is almost always used as a local or loco-regional therapy in animals. The exceptions to this are half-body and whole-body RT, which are under investigation at a number of institutions for the treatment of lymphoma in dogs, but will not be discussed further in this article. Therefore, in all of the situations discussed above, RT is used for treatment of the primary tumor and has little or no effect on regional or distant metastases that are outside of the treatment field. This is important to keep in mind when considering the use of radiation in the treatment of tumors that have a moderate to high metastatic potential.

Side Effects

The side effects of RT are primarily limited to the normal tissues that are included within the radiation field. However, if they involve a significant amount of normal tissue or if they become severe, then they can be life threatening or significantly degrade a patient's quality of life. The fractionation scheme and targeting of the radiation to the tumor can be optimized to minimize the risk of severe, potentially permanent, late effects. However, there are typically always some side effects in radiation patients and, therefore, it is important to be able to identify these and take measures to prevent or manage them when they do occur.

Acute Radiation Side Effects

The side effects of RT are divided into acute and late side effects based on when they occur relative to RT. Acute side effects typically are first observed during RT (eg, toward the end of the second week of a daily RT protocol), and will progress for the first 7 to 10 days after the end of RT before they start to resolve. Acute radiation side effects occur primarily in renewing tissues that have rapidly dividing cells such as the oral mucosa, skin, etc. RT protocols that use small, daily doses of radiation commonly result in significant acute effects that can be problematic during and immediately after therapy. Although acute effects can cause discomfort for the patient, it is important to remember that they are self-limiting and, therefore, usually do not impact the decision-making process when deciding on a treatment protocol. However, full-course RT typically is not recommended for patients likely to succumb to their disease in a matter of a few months because the acute adverse effects will persist for 4 to 6 weeks and will have a negative impact on

TABLE 2. Select Potential Side Effects of Radiation Therapy on Normal Tissues

Tissue	Acute Side Effects	Late Side Effects
Skin	Erythema Alopecia Dry or moist desquamation	Fibrosis Contraction Non-healing ulcer Leukotrichia
Oral cavity	Mucositis Salivation Halitosis	Bone necrosis Periodontal disease Xerostomia
Nasal cavity	Rhinitis Nasal discharge	Chronic discharge
Eye	Keratitis/corneal ulcer Conjunctivitis Blepharitis/blepharospasm Uveitis	Cataract Keratoconjunctivitis sicca
Cervical region	Pharyngitis Esophagitis Tracheitis	Hypothyroidism Esophageal stricture
Intestinal Tract	Colitis Enteritis	Stricture
Foot	Pad slough Lost or deformed nails	Lost or deformed nails
Spinal cord	Inflammation Edema	Myelopathy Infarction
Brain	Inflammation Edema	Encephalopathy Infarction Hemorrhage
Kidney	Nephritis	Fibrosis Decreased function
Bladder	Cystitis	Fibrosis

quality of life during that time period. Select tissues that typically exhibit acute radiation side effects are listed in Table 2. Certain management practices may help decrease the severity and duration of acute radiation side effects in patients undergoing treatment. For example, prophylactic dental cleaning before RT can help prevent the development of oral ulcers when the treatment field involves the oral cavity. Also, prophylactic use of anti-inflammatory doses of glucocorticoids may help decrease the severity of acute side effects involving any treated tissue. Patients are also typically placed on oral antibiotics to help prevent secondary infections.

Late Radiation Side Effects

Late side effects are caused by damage to the supporting stroma or vasculature that supplies an area or tissue. Late effects are typically in nonrenewing tissues such as nerve and bone, but may occur in skin and other tissues and, in this instance, are related to the severity of the acute reactions (referred to as consequential late effects). Damage to the tissue or vasculature can lead to tissue fibrosis or necrosis, as well as infarction. Late effects usually occur 6 or more months after a course of RT. Another late effect that can occur is the development of a radiation-induced tumor in the radiation treatment field, with an onset of occurrence 3 to 5 years after RT. The incidence of radiation-induced tumors in veterinary patients has not been defined, but is presumably low, in part due to the fact that many of the patients do not live long enough for a radiation-induced tumor to become manifest. Late effects can occur in any tissue. The most significant problem is that late effects are usually difficult to manage, may be permanent, and therefore should be avoided whenever possible. In general, treatment with larger doses of radiation, such as those used in PTRT, is more likely to result in late side effects. However, in most patients that are treated with PTRT, palliative therapy is chosen because they have a poor prognosis due to the nature of the tumor type or presentation, or to the presence of metastasis at the time of RT. In such patients, late radiation side effects are less of a concern due to their limited expected survival. The best approach for managing late radiation side effects is to prevent them from occurring. Therapeutic intervention may be possible for select late effects, such as cataract surgery for cataracts, bougienage for stricture of hollow viscera, and debridement for bone necrosis.

Conclusion

RT can be a very effective treatment for small animal cancer patients. Technological advances continue to allow for safer and more accurate delivery of radiation, resulting in improved tumor control and decreased incidence of radiation-induced side effects. As our understanding of the effects of radiation on animal tumors continues to expand, we are learning the best ways to utilize radiation alone or in combination with other treatment modalities. These improvements, combined with the increased availability of radiation, have made this treatment modality one that is likely to continue to be sought out by pet owners, and recommended by veterinarians for many cancer patients. Radiation can play a role in the treatment of a wide variety of tumor types. Palliative or definitive treatments may be indicated depending on the clinical scenario and the goals of the individual pet owner. To be able to try to attain these goals requires an understanding of the types of radiation that are available, the indications or potential uses of radiation, and also an understanding of the potential adverse effects related to treatment.

Reviews of the indications and outcomes of RT have been published in veterinary oncology textbooks.[1,46] Consulting with a veterinary radiation oncologist and/or medical oncologist is recommended when considering RT for a pet with cancer. An initial discussion may provide adequate information to make an initial decision as to whether or not to suggest radiation as a treatment option. However, an appointment and consultation with a veterinary oncology specialist may still be necessary before a decision can be made.

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