VETERINARY RADIATION THERAPY: Innovations and Indications

Jessica Lawrence DVM DACVIM (Oncology) DACVR (Radiation Oncology)

UNIVERSITY OF MINNESOTA
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INTRODUCTION

Cancer is the leading natural cause of death in cats and dogs and the prevalence of cancer in pet animals is rising. Cancer is not simply one disease, but many different diseases with various biologic behaviors, standards of care and prognoses. There are many misconceptions about treatment options and the quality of life of companion animals living with cancer but it is our role as veterinarians to be compassionate and knowledgeable resources for our clients/patients.

Background

Radiation therapy (RT) began in the 19th century, following Roentgen's description of x-rays in 1895 and the discovery of radium by Marie & Pierre Curie in 1898.[1-3] Radiation oncology now refers to the medical use of ionizing radiation (IR) as an integral part of cancer treatment by killing or controlling malignant cells. The primary purpose of RT has remained to provide local and/or loco-regional treatment, although half body or total body irradiation is occasionally administered. Depending on the clinical situation, the primary intent of treatment is either palliative or definitive (potentially curative) and is commonly used in conjunction with other therapies such as surgery and/or systemic therapy. RT has been available in a number of veterinary facilities for over 30 years and the number of units and degree of sophistication continually grows.[4-6]

Considerations When Choosing Veterinary Patients for Radiation Therapy

Dogs and cats (and occasionally other species such as rabbits) should be evaluated carefully prior to offering radiation therapy in order to ensure that they are good candidates. It is important to understand the tumor type, biologic behavior and extent of disease to determine if radiation therapy is indicated and likely to aid in control. Radiation therapy alone or in combination with surgery may be a very appropriate treatment modality to manage patients with local or loco-regional disease; adjuvant chemotherapy can also be administered concurrently. Prospective planning often involves a coordinated patient care team including surgeons, medical oncologists, and radiation oncologists to determine the best approach to managing a tumor. A good option for one patient may not be suitable for another patient despite a similar tumor histology.

Staging, or a determination of the extent of cancer, is important in order to determine if localized disease is present. Diagnostic tests typically relate to the primary tumor type and may include complete blood count, biochemical profile, urinalysis, aspiration cytology of regional lymph nodes, thoracic and/or abdominal imaging, and advanced imaging. Computed tomography (CT) is one of the most useful tools for tumor imaging as it is critical for computer-assisted radiation treatment planning. Based on CT images, subjective initial assessments can be made regarding extent of disease, proximity of critical tissues near or in the treatment field (such as the eyes in the case of dogs with nasal tumors), and prognosis.

RADIATION PHYSICS: HOW DOES RADIATION INTERACT WITH TISSUE?

Ionizing radiation (whereby an atom loses an electron and becomes ionized) consists of both x-rays and γ-rays: x-rays are man-made and arise from a linear accelerator (or diagnostic x-ray unit) while γ-rays occur from radioactive decay (^{60}Cobalt). With low energy photons (diagnostic), photons are absorbed differentially in tissue, which is dependent on the density of the tissue. This photoelectric effect is what provides the differentiation between bone, soft tissue, and fat on a diagnostic radiograph. With high-energy electrons (therapeutic), physical interactions with tissue occur predominantly via Compton scattering, which minimizes the differential absorption across various tissues to provide more uniform dose.

RADIATION BIOLOGY: HOW DOES RADIATION INDUCE DAMAGE?

High-energy photons from a linear accelerator collide with orbiting electrons of biologic molecules in tissue, which leads to the ejection of electrons. These electrons can directly damage biologic targets (such as DNA) or, more commonly, interact with water (cells are made up of 80% water) to produce free radicals that damage the target (indirect damage). Photons are considered "skin-sparing", as there is a buildup region of tissue needed for maximum radiation dose. Electrons from a linear accelerator can also be used for treatment, as they act like the secondary electrons created by high energy x-rays. DNA within tumor cells is generally considered to be the principal target of therapeutic photons, although damage to cell membranes and blood vessels may also contribute to tumor control.[1-3] Oxygen essentially "fixes" radiation damage to DNA while certain phases of the cell cycle are more sensitive to radiation. [1] Both the oxygen effect and the reassortment of the cell into a sensitive phase of the cell cycle provide a basis for fractionating radiation – or dividing up the overall dose into many doses.

Several consequences can occur in the cell after DNA damage. Cells can repair DNA damage if enough time is present after radiation delivery, whereas other cells (lymphocytes, mast cells) die instantly from receiving a "hit" of radiation. The most common consequence is a disruption in mitosis (cell division) that ultimately triggers cell death.[1] <u>Radiation is generally more effective on microscopic disease compared to macroscopic tumors although there are exceptions depending on the tumor type. As most cells sustain "reproductive" damage, measurable tumors often do not shrink immediately but may respond after several weeks of RT</u>.

RADIATION THERAPY

Radiation Terminology

Radiation terminology can be confusing and some terms (SRS and SRT) are inaccurately used as synonyms. Common terminology and abbreviations are provided below.[1-5]

Dose – amount of radiation absorbed by the patient (Gray=Gy= 1 Joule/kg; the older term "rad" is no longer used)
Fraction – individual administration of radiation
Fractionation – radiation dose is divided into fractions over the course of several days to weeks
Protocol – particular dose and number of fractions to be given to a particular tumor
External beam radiation – radiation delivered from outside the body by a machine that focuses high-energy photons at a tumor
3-D Conformal RT (3D-CRT) – conformal radiation therapy that is image-based and improves radiation dose distribution across the tumor volume, which can limit the normal tissue involved
Intensity-modulated RT (IMRT) – improved radiation planning and delivery to change the intensity of the radiation beams aimed at the target volume to improve conformity of the radiation dose distribution to tumor with a rapid fall-off in radiation dose to adjacent normal structures
Image-guided RT (IGRT) – allows the detection of patient and tumor positioning errors through the use of advanced images acquired prior to each treatment (usually IMRT treatments). IGRT provides a "quality assurance" that the radiation beams are directed precisely to the target volume (tumor)
Stereotactic radiosurgery (SRS) - single treatment involving a large fraction size (15-20 Gy), usually to treat small well-delineated tumors
Stereotactic radiation therapy (SRT) - a small number of treatments (3-8) involving a large fraction size (10-20 Gy) used to treat small well-defined lesions

Clinical Radiation Therapy

The primary goal of radiation therapy is to precisely target the tumor volume with "tumoricidal" doses of radiation while minimizing dose to surrounding normal structures. This involves multiple steps in order to ensure the tumor volume is adequately treated. The overall dose and fractionation protocol is largely based on the particular tumor type and grade, adjacent normal tissue, the inherent radiosensitivity of the tumor cells, clinical evidence, and clinical experience. Advanced imaging (CT) aids in the delineation of tumor volumes and target structures. Typically a radiation oncologist outlines 3 main tumor volumes as well as normal tissues (organs at risk) within the imaging. Tumor volumes include: gross tumor volume (GTV), clinical target volume (CTV) to account for microscopic disease, and planning target volume (PTV) to account for intrinsic and extrinsic setup error. The radiation prescription is typically prescribed to the PTV and thus it is important to recognize what the PTV might encompass. Developments in computerized treatment planning have vastly improved the ability of the radiation oncologist to target the tumor and reduce the radiation dose to normal structures.

Normal Tissue Toxicity

Animal owners, veterinarians and veterinary technicians are correct to be concerned about the development of toxicity and it is important that a thorough discussion occurs between all parties prior to starting radiation therapy. Treatment toxicity depends on the fractionation schedule, the time over which radiation occurs, and the normal tissues that are in the radiation field. Radiation can damage any cell (normal or cancer) but therapeutic radiation attempts to exploit the difference in repair capabilities between normal and tumor tissue.[1-3] Tumor cells do not repair as well as normal cells, so fractionating radiation is intended to allow damage to accumulate in tumor cells while normal cells repair. Cell killing is exponential; therefore large tumors require higher doses of radiation to induce a complete response compared to smaller tumors. [1-5]

Normal tissue in the radiation field is "dose-limiting" with respect to the maximum dose that can be safely administered. The dose per fraction, treatment schedule, and total dose affect the tolerance of the normal tissues. Fractionation refers to the delivery of smaller doses of radiation a number of times in order to reduce the toxicity to normal tissues and often to improve the overall response of a tumor. Giving radiation once or twice a day allows normal cells to repair but does not provide adequate repair of tumor cell damage. The probability of tumor control is always weighted against the probability of complications.

<u>Acute radiation toxicity is typically reversible and self-limiting and occurs during or shortly after therapy; effects are confined to the irradiated area</u>. Rapidly proliferating tissues such as epithelium, mucosa, and tumor cells are affected most in the acute setting. Discomfort is expected in the short-term and early effects can be unpleasant for both the owners and the pet. Acute toxicities are predominantly dependent on the total dose of radiation administered (the higher the dose, the greater the toxicity) but also on the duration and frequency of treatment (shorter overall treatment time increases toxicity) and the fraction size (the higher the fraction size, the greater the toxicity).[1-3]

<u>Late radiation side effects are typically adverse events that occur 6 months or greater after completion of radiation therapy and are related to the structures within the irradiated field</u>. Late effects typically develop in non-renewing tissues such as nerve, bone, and muscle. These non-renewing tissues are dose -limiting; dose to tumor is typically prescribed such that the probability of the occurrence of clinically-relevant late effects is < 5%. Late tissue damage is progressive and irreparable in most cases and results from vascular damage, fibrosis, and loss of cells. The likelihood of late radiation effects is heavily dependent on the size of the fraction (the greater the fraction size, the greater probability of late toxicity), although the overall dose prescribed is also important.

Radiation Protocols

Factors that dictate the likelihood of late toxicity support the rationale behind choosing definitive versus palliative radiation protocols for a particular case.

<u>Definitive radiation protocols</u> are typically administered daily (Monday through Friday) for 2-4 weeks in a row depending on the underlying tumor type. In the author's practice, definitive protocols are recommended for pets with a good prognosis and that have a high likelihood of survival beyond 6 months. The dose given each day in this type of protocol is lower in order to "protect" normal tissue from developing significant late toxicities that could negatively impact quality of life.

<u>Palliative protocols</u> are typically reserved for animals with a poor prognosis. The goals of palliative therapy are to alleviate pain associated with the tumor, decrease the size of any mass causing obstruction (a laryngeal mass), and to otherwise alleviate debilitating signs of cancer (bleeding from a large ulcerated oral mass). Palliative radiation therapy is not intended to prolong survival (although indirectly often prolong survival) but to improve the quality of life for the time remaining. There are many different protocols for palliative radiation however they often involve radiation administered once weekly or twice weekly for 4 doses or for 4-5 total doses administered daily. Because the dose of radiation is higher for each fraction, if pets do well (> 6 months) with treatment, there is a higher likelihood of clinically relevant late toxicity.

Most tumors are ideally treated in the microscopic disease setting; therefore postoperative therapy is most common, when surgical margins are incomplete or narrow. However, there are situations in which preoperative radiation therapy is indicated. Cats with injection site sarcomas often have extremely large tumors (the "tip of the iceberg" effect) that are best treated with preoperative radiation followed by aggressive surgical resection. Occasionally dogs with unresectable tumors can be managed as cats with injection site sarcomas. Many tumors are responsive to radiation, however the overall response tends to be variable and dependent on the signalment, tumor histology, location, grade, and/or stage of disease. It is always important to remember that normal critical structures adjacent to the radiation field limit the amount of radiation that can be administered; occasionally doses must be modified to avoid significant injury. A general guide for tumor types that are responsive to radiation is provided in Table 1.

Table 1: Common tumor types in dogs and cats and respective radiation responses[4,5]

Tumor	Response to radiation
Ameloblastoma (Acanthomatous epulis)	Excellent
Oral Fibrosarcoma	Poor to fair
Oral Melanoma	Fair to good local control
Oral Squamous Cell Carcinoma (dog)	Good
Oral Squamous Cell Carcinoma (cat)	Poor
Nasal Adenocarcinoma	Good
Nasal Sarcoma	Good
Nasal Poorly Differentiated Carcinoma or Squamous Cell Carcinoma	Poor to fair
Mast Cell Tumor	Good to excellent
Lymphoma (localized)	Excellent
Perianal Gland Adenoma	Excellent
Anal Sac Apocrine Gland Adenocarcinoma	Good to excellent
Perianal Gland Adenocarcinoma	Good
Salivary Gland Adenocarcinoma	Good to excellent
Squamous Cell Carcinoma (non-oral)	Poor to fair
Thyroid Carcinoma	Good
Multilobular Osteochondrosarcoma (MLO)	Unknown – fair?
Brain Tumors	Poor to good
Soft Tissue Sarcoma	Good to excellent
Osteosarcoma	Good (palliative)
Prostatic Adenocarcinoma	Poor to Fair
Transitional Cell Carcinoma	Poor to fair

Summary

Radiation therapy is appropriate for a number of different scenarios including: 1) potentially any single site disease, 2) in the pre-surgical or post-surgical setting, 3) radioresponsive tumors in the gross (measurable) disease setting 4) palliation of pain or temporary local control to improve function. Generally speaking, tumors will be more responsive to radiation in the microscopic disease setting, thus surgery is often indicated first. It is important to differentiate the goals of radiation treatment and to be prepared for relevant acute and late toxicities.

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Radiation Therapy

University of Minnesota
Veterinary Medical Center

Cancer In Pets

Cancer is the uncontrolled growth of abnormal cells on or in the body. Cancer in pets is a relatively common disease and is the leading cause of death in pet dogs and cats. Not all cancer is the same but many types are treatable. In some cases we are able to control the cancer long term with specialized cancer care. Treatments offered for cancer in humans is becoming increasingly available for pets, including radiation therapy. While radiation therapy is not recommended for every pet, you may wish to learn more about options that may be recommended to treat your pet's cancer.

What Is Radiation Therapy?

Radiation therapy uses ionizing radiation to induce DNA damage within cancer cells, which ultimately results in cancer cell death. External beam radiation therapy using a linear accelerator (linac) is the most common type of radiation therapy, in which radiation beams are shaped to the aim at the pet's tumor or surgical scar while avoiding as much normal tissue as possible. Most pets are anesthetized for each treatment and carefully positioned on a treatment couch (table). It is common for pets to need a CT scan in order to determine the extent of tumor and to help devise a pet-specific radiation treatment plan. This may be needed even if a CT has been done previously for diagnosis or staging, in order to optimize your pet's radiation plan.

Radiation Therapy Goals

Radiation therapy is typically administered to localized tumors with the primary goal of achieving long term tumor control while minimizing any radiation injury to normal structures. It is most often used after surgery for incompletely excised tumor, where there is a reasonable risk of local tumor recurrence, but may be considered prior to surgery in some cases. Radiation therapy administered in this manner is often called definitive-intent radiation therapy (sometimes curative-intent), as it aims to achieve long-term control of tumors. Most veterinary radiation patients undergoing definitive intent radiation are treated over a 3-4 week period, with a small fraction (dose) of radiation administered daily through the week. New technologic advancements have enabled modified protocols in which 1-7 large fractions of radiation are administered instead of many smaller doses; however, this is limited to practices with specialized radiation equipment (stereotactic radiosurgery or stereotactic radiation therapy).

Palliative radiation therapy has a different goal in that it may help relieve pain or improve function for pets with advanced cancer. These protocols can vary and may involve one treatment given weekly or treatments given over several days in a row. The duration of tumor control is much shorter than with definitive intent radiation therapy, however often helps to improve quality of life. Generally palliative radiation therapy is reserved for patients with advanced disease due to a higher risk of radiation damage to normal tissues when compared to definitive protocols.

What is My Pet's Quality of Life During Radiation Therapy?

Oncology teams make every effort to ensure that pets are comfortable and happy during treatment with excellent quality of life. With definitive-intent protocols, acute side effects in the irradiated site (such as radiation burn to the skin or mouth) may occur but are managed with supportive care and tend to heal quickly following treatment. The likelihood of acute effects is dependent on the location of the tumor and the radiation protocol. Late radiation effects may also occur, which are permanent irreversible changes to irradiated tissue that occur months to years following radiation therapy. Most late effects are mild and may include effects such as haircoat color change or permanent loss of hair. It is important to discuss potential side effects with your pet's oncologist or radiation oncologist prior to therapy so that you know what to expect with treatment. Because palliative radiation therapy is administered with a different goal, acute side effects are rare but the potential for significant late effects is higher; however, as palliative radiation is typically reserved for advanced cancer, late effects are rare.

Pets undergoing radiation therapy are welcome to go home each day, but many pets can board in the hospital while they receive treatment.

What Tumors Are Commonly Treated With Radiation Therapy?

Many tumors can be treated with radiation therapy; the most common tumor types in dogs and cats include nasal tumors, brain tumors, spinal cord tumors, tumors of the skin (mast cell tumors, soft tissue sarcomas, injection site sarcomas), tumors in the mouth, anal sac tumors, and bone tumors.