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CONTINUING EDUCATION

ONCOLOGY

Conventional Versus Stereotactic Radiotherapy

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Although radiotherapy is among the oldest cancer treatment modalities, significant advancements in its planning and delivery that have taken place in the last 20 years have translated to advancements in veterinary radiation oncology. This article will describe radiotherapy treatment with a linear accelerator (LINAC), as this is the most common radiotherapy delivery method used in veterinary medicine.

THE MODERN RADIOTHERAPY PLANNING AND DELIVERY PROCESS

Patient Assessment

When a patient is referred for radiotherapy, the veterinary radiation oncologist reviews the biopsy results, performs a physical examination, reviews any images, and localizes the anatomy of the tumor to be treated before performing a computed tomography (CT) scan of the patient and the anatomic area affected. The CT scan can be used for diagnostic purposes as well as for radiotherapy simulation purposes. If advanced imaging and staging have already been completed, a simulation-only CT study may be performed. For instance, many patients that are referred to a radiation oncologist for a brain tumor have had a magnetic resonance imaging (MRI) scan completed to make the diagnosis. Positional devices such as thermoplastic masks, vac-lock bags, and alpha cradles are used during simulation so that when the patient is treated

BOX 1 Understanding Radiotherapy Prescriptions

Each radiotherapy treatment session is called a fraction. The radiotherapy prescription (total prescribed dose and prescribed dose per fraction) is administered in a unit called a Gray (Gy). A Gray is a unit of absorbed radiation dose in joules/kg of water. So, if a patient is prescribed a total dose of 20 Gy in 4-Gy fractions, the prescription may be written as 4 Gy × 5 fractions.

THE GOOD FIGHT
Stereotactic radiotherapy is a powerful cancer treatment technique, but care must be taken in patient selection, treatment planning, and radiation delivery to avoid late side effects.

FIGURE 1. Positioning devices used for radiation therapy simulation and to help reproducibly position patients with tumors affecting different anatomy. Accurate positioning allows for accurate modeling of the patient anatomy and ultimately the dose distribution. **(A)** Thermoplastic mask and bite plate with maxillary dental impression for head and neck tumors. **(B)** Alpha cradle device used for positioning patients with tumors in or on the body. **(C)** Vac-lock bag used for positioning patients with tumors in or on the body. **(D)** 3-D model of a patient positioned in a thermoplastic mask and bite plate. **(E)** Patient immobilized for stereotactic radiation therapy of a nasal tumor. The maxilla is affixed to a bite plate and the head is secured to the table with a custom thermoplastic mask.

several days later, its simulation position is accurately reproduced (**FIGURE 1**). The radiotherapy prescription and technique are typically decided just prior to CT simulation or very soon after, depending on the extent of the tumor, the anatomy affected, the condition of the patient, and a discussion with the owner (**BOX 1**).

Treatment Planning

After the CT scan is imported into the radiotherapy planning system, the radiation oncologist contours (draws) the tumor and normal anatomy using planning software. When contouring is completed, the radiation oncologist uses the planning software to target the radiotherapy beam to the tumor while trying to spare normal tissues from irradiation as much as possible. A radiotherapy simulation CT scan accurately models the geometry of the patient and the distribution of the radiation dose inside the patient. Accurate positioning and modeling of the dose distribution are extremely important to the successful delivery of radiotherapy and minimization of side effects.

Technology

After radiotherapy planning is completed, each fraction is administered using the radiotherapy machine (LINAC). LINACs are capable of rotating around the patient table and delivering a beam of radiation from any angle to a calibrated fixed point called the isocenter. The radiotherapy beam is shaped by a collimator inside the LINAC. Most modern linear accelerators have a multileaf collimator (MLC), which can make geometrically rectangular shapes (solid jaws) and contains independently moving leaves that span the width of the solid jaws (**FIGURE 2**). MLC leaves are typically 2.5 to 10 mm in width and can make a fixed aperture to block out organs such as the eye or brain.

Some LINACs can move their MLC leaves dynamically while the treatment beam is turned on to sculpt the dose of radiation around complex structures in a technique called intensity-modulated radiation therapy (IMRT). More recently, LINACs capable of moving MLC leaves dynamically while also rotating the gantry have become available; use of this technique is called

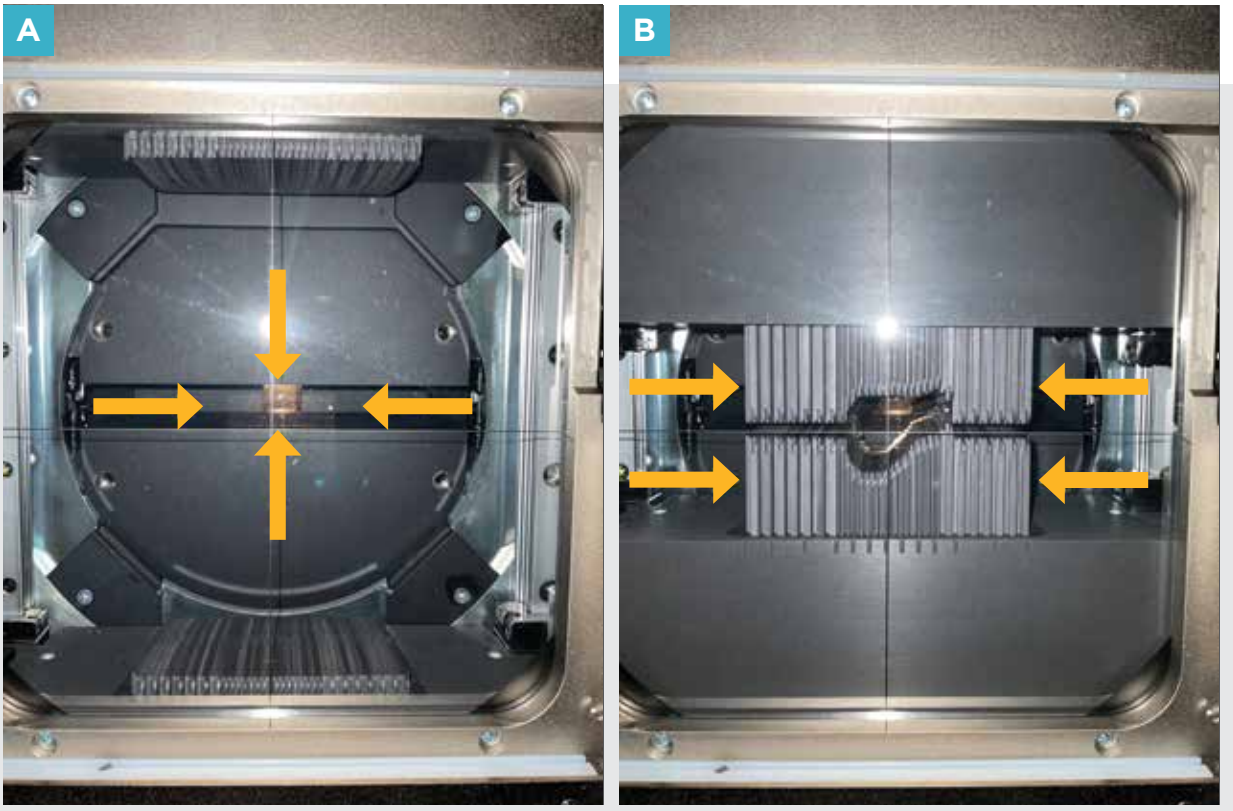

FIGURE 2. (A) Solid collimator jaws in the treatment head of a modern linear accelerator **(yellow arrows)**. The solid jaws can shape the radiation beam into rectangular shapes. **(B)** The multileaf collimator **(yellow arrows)** positioned to shape the beam for a feline urinary bladder. The leaves on this machine are 2.5 mm in width at the center and 5 mm in width on the outer boundaries of the multileaf collimator.

A main difference between IMRT and VMAT is that the LINAC gantry does not move while administering radiation during IMRT treatment.

volumetric modulated arc therapy (VMAT). A main difference between IMRT and VMAT is that the LINAC gantry does not move while administering radiation during IMRT treatment. IMRT and VMAT can create similar dose distributions; the main advantage of VMAT is faster delivery time. **FIGURE 3** illustrates the difference in dose distribution between a patient treated using a fixed-aperture technique and MLC and a patient planned with VMAT.

Treatment Administration

Prior to each treatment session, the patient is placed in its positional device and the radiation beam is aligned to the tumor and the positional device by moving the radiotherapy table to align with lasers mounted in the treatment room. Depending on the anatomic location of the tumor and treatment technique used, imaging using the radiotherapy machine may be performed to verify the patient's position and the aiming of the LINAC at the tumor. A fixed-aperture technique targeting a tumor or scar on a distal extremity may not require any pretreatment imaging as the collimator and beam alignment can be visually matched to this simple anatomy. A brain tumor treated with stereotactic radiotherapy (SRT) requires imaging prior to administration. Pretreatment imaging is typically accomplished using a cone beam computed tomography (CBCT) scanner mounted to the radiation therapy machine. The CBCT image is compared with the simulation image and the table is robotically moved to align the patient so that the treatment position matches the simulation position with submillimeter accuracy.

CONVENTIONAL RADIOTHERAPY OVERVIEW

Conventional palliative radiotherapy (cPRT) protocols and conventional definitive radiotherapy (cDRT) protocols were developed soon after the discovery of the x-ray and are still widely used today. These treatments exploit the tolerance of normal tissues to radiotherapy and the relative sensitivity of cancer cells. cPRT uses large fraction sizes and a lower total dose of radiation, while cDRT uses smaller fraction sizes and a higher total dose. Tumor control and side effects that result from irradiation of normal tissues depend on the radiation dose received by those structures. Prescriptions are designed to avoid adverse effects.

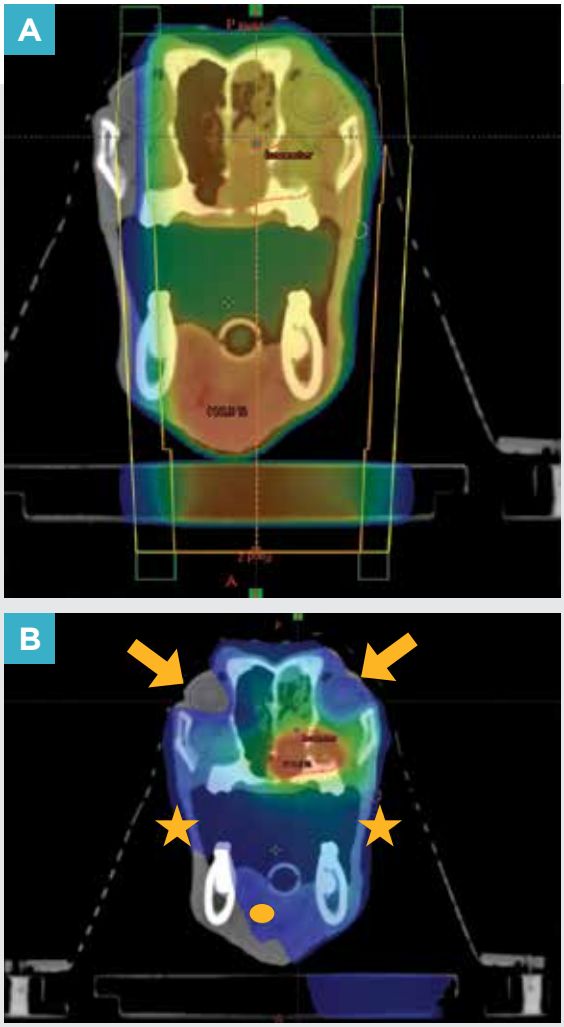

FIGURE 3. (A) Dose distribution of a nasal tumor planned with a fixed multileaf collimator 3-D plan. The areas of red and yellow represent areas of high radiation doses (greater than 95% of the prescription). The areas of blue represent areas of low radiation dose (less than 20% of prescription). **(B)** Dose distribution of the same nasal tumor planned with volumetric modulated arc therapy. Red and blue areas represent areas of high and low dose as in **(A)**. Note the sparing of normal tissues such as the tongue **(yellow oval)**, eyes **(yellow arrows)**, and lips **(yellow stars)**.

Conventional radiotherapy treatments are nonablative and are not intended to remove or destroy the function of the normal tissues in the treated volume. However, this does not mean that durable remission or cure is impossible with cDRT. When normal tissues in the treatment field are exposed to high total doses of radiation, doses must be fractionated because normal tissues tolerate smaller doses per fraction better. Therefore, to deliver a high total dose of radiation to sterilize tumor cells when normal tissues are also exposed, the radiation must be delivered as multiple daily treatments over weeks.

Conventional Palliative Radiotherapy

The goal of cPRT is to relieve pain and discomfort without administering a total dose of radiation that causes clinically significant acute side effects. Survival times with cPRT may be longer due to increased quality of life; however, survival is not the main emphasis or goal. Large fraction sizes (4 to 8 Gy) given over 4 to 5 fractions are typical palliative-intent radiotherapy prescriptions. Most patients that are candidates for palliative radiotherapy must have a grossly visible mass or lesion to treat. Pets that are candidates for palliative radiotherapy should have a guarded long-term survival prognosis (less than 6 to 8 months) due to the large fraction size and concerns for causing irreversible late side effects in normal tissues.

Conventional Definitive Radiotherapy

The goal of cDRT is to achieve durable long-term remission and survival. cDRT protocols attempt to deliver the highest total dose of radiation that the normal tissues adjacent to the treated area will tolerate. In many cases the treated volume is an area of apparently normal tissue with microscopic tumor infiltration. A prescription of 3 Gy × 19 fractions given Monday through Friday is an example of a typical

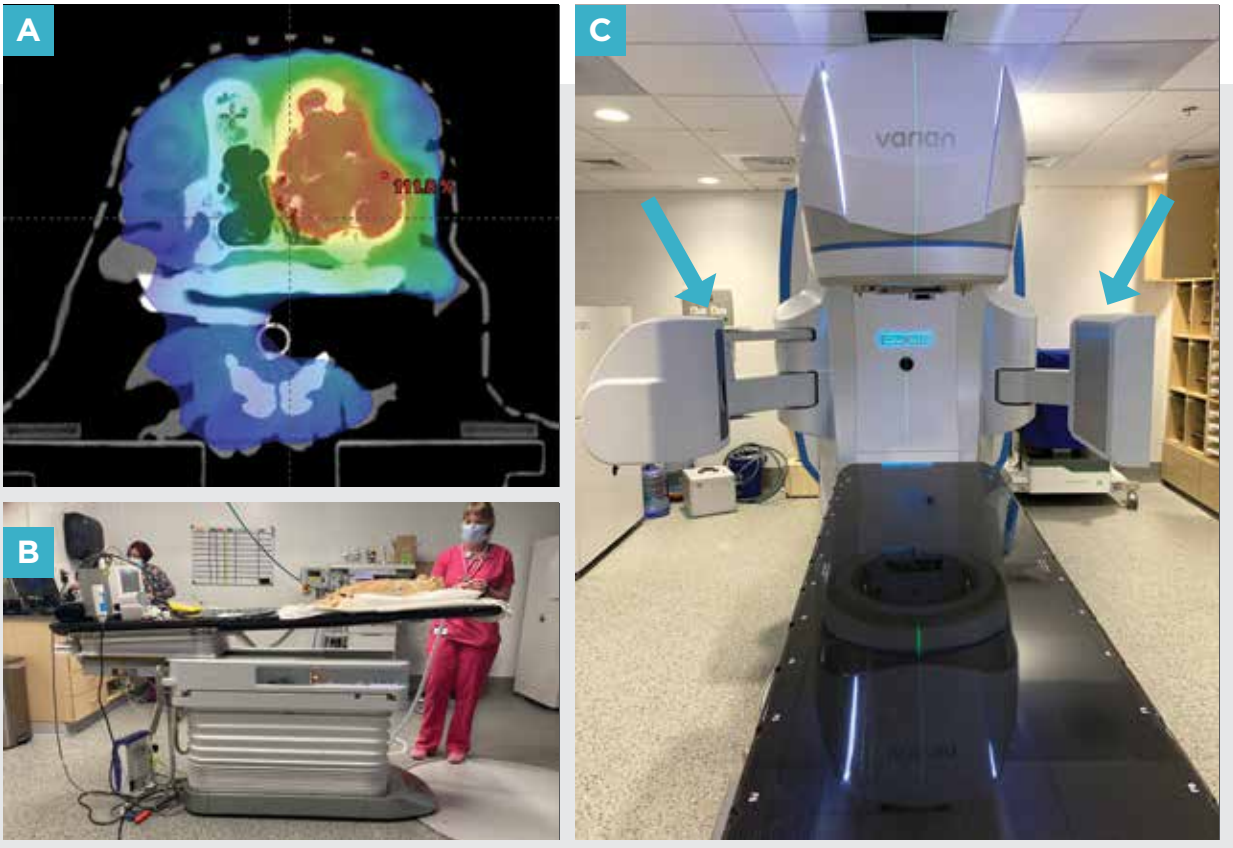

FIGURE 4. (A) Computed tomography scan and color wash showing volumetric modulated arc therapy dose distribution in a patient treated with 15 Gy × 1 fraction stereotactic radiation therapy (SRT) for a nasal tumor. Reds indicate tissues receiving 95% of the prescription; greens, 50% of the prescription; and blues, less than 20% of the prescription. **(B)** Robotic positioning unit for a linear accelerator designed for SRT. The table can pivot and adjust up to 3 degrees pitch/roll (as shown). **(C)** Linear accelerator gantry (center) cone beam computed tomography unit **(arrows)** allows for 3-D imaging with the patient in position for treatment and matching the table in **(B)** to properly align the radiation beam.

Acute radiation side effects occur in rapidly proliferating normal tissues of self-renewal (e.g., skin, oral mucosa, gastrointestinal tract), are usually reversible, and are not the dose-limiting toxicity.

definitive-intent radiotherapy prescription. Patients that have soft tissue sarcomas or mast cell tumors of the extremities that were removed with concern for microscopic disease in the scar bed are examples of cDRT candidates. Definitive intent radiotherapy can also be used for gross disease in patients with nasal, brain, or thyroid tumors.

Side Effects

Depending on the technique used to administer cDRT and the area being treated, acute treatment-related side effects may be expected. Superficial scars, as in the example of an incompletely resected soft tissue sarcoma on the extremity, are expected to develop moderate to severe moist desquamation 2 to 3 weeks into their course of treatment. Dogs or cats with brain tumors or pituitary tumors would be unlikely to develop painful acute side effects in superficial normal tissues because the radiation is focused on deeper tissue in the brain.

Acute radiation side effects occur in rapidly proliferating normal tissues of self-renewal (e.g., skin, oral mucosa, gastrointestinal tract), are usually reversible, and are not the dose-limiting toxicity. Acute side effects are a clinical and quality-of-life concern during and for a short time after the completion of cDRT or cPRT; they are expected to resolve with time and supportive care.

In contrast, late side effects of radiotherapy are the major dose-limiting toxicity and are of significant

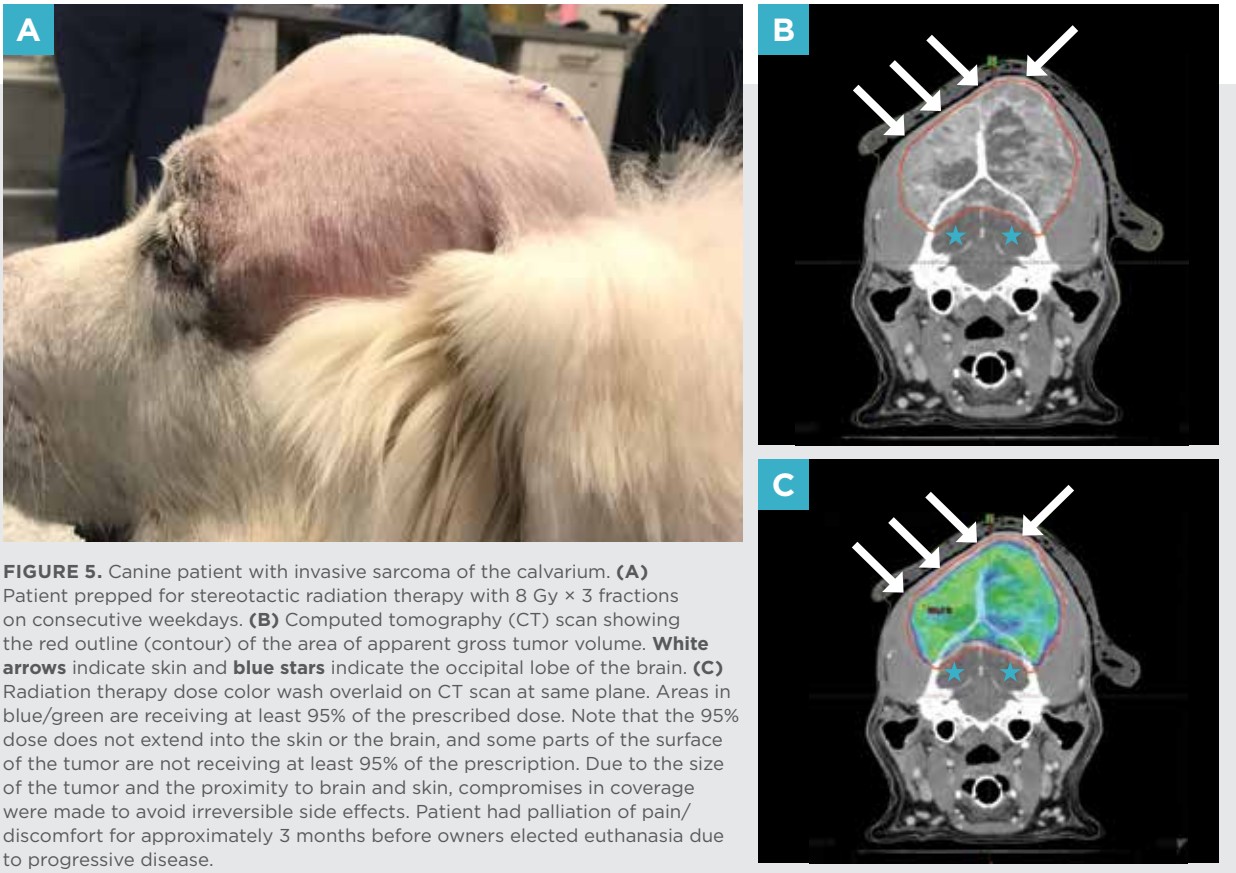

FIGURE 5. Canine patient with invasive sarcoma of the calvarium. **(A)** Patient prepped for stereotactic radiation therapy with 8 Gy × 3 fractions on consecutive weekdays. **(B)** Computed tomography (CT) scan showing the red outline (contour) of the area of apparent gross tumor volume. **White arrows** indicate skin and **blue stars** indicate the occipital lobe of the brain. **(C)** Radiation therapy dose color wash overlaid on CT scan at same plane. Areas in blue/green are receiving at least 95% of the prescribed dose. Note that the 95% dose does not extend into the skin or the brain, and some parts of the surface of the tumor are not receiving at least 95% of the prescription. Due to the size of the tumor and the proximity to brain and skin, compromises in coverage were made to avoid irreversible side effects. Patient had palliation of pain/discomfort for approximately 3 months before owners elected euthanasia due to progressive disease.

concern because they are not reversible. Late side effects occur in slowly proliferating normal tissues such as bone, nerves, and muscle. Examples include bone necrosis and stricture formation or perforation in tubular organs. Second cancers are also considered late side effects of radiotherapy. Late radiotherapy side effects may appear 6 months to a year or longer after completion of radiotherapy. Slowly proliferating normal tissues have a limited capacity for self-renewal, and their sensitivity to late side effects increases exponentially with the size (in Grays) of each radiotherapy fraction. Late side effects do not spontaneously resolve, are nonhealing, and are potentially life-threatening for the patient; therefore, they must be avoided when normal tissues are exposed. They can be avoided with appropriate treatment planning and fraction size selection.

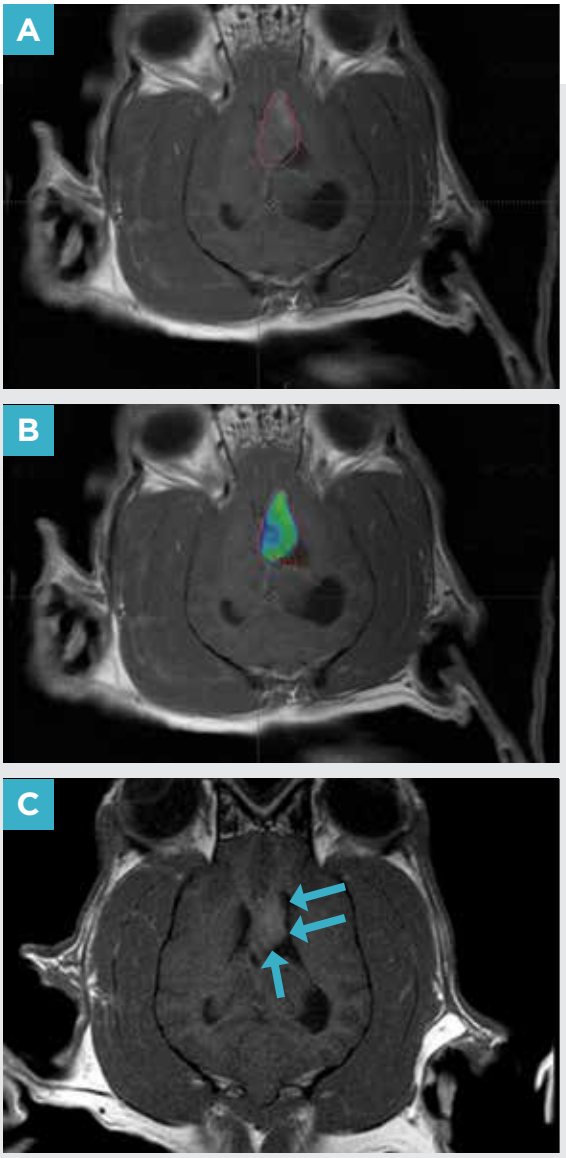

FIGURE 6. (A) T1 + contrast dorsal plane brain magnetic resonance imaging (MRI) scan of a dog with suspected ependymal tumor of the lateral ventricle **(red circle)**. **(B)** Radiation therapy color wash at same plane as **(A)**. Patient was prescribed 8 Gy × 3 fractions of stereotactic radiation therapy (SRT) on consecutive weekdays. Blue-green area is receiving at least 95% of the radiation prescription. Note how coverage of the surface of the mass **(red circle)** is much better than the case in **FIGURE 3**. Smaller tumors can receive a more homogenous dose than larger tumors, as it is easier to avoid normal tissues. **(C)** T1 + contrast dorsal plane brain MRI of same dog 3 months post-SRT, showing significant shrinkage of the mass **(blue arrows)** but not complete remission.

STEREOTACTIC RADIOTHERAPY OVERVIEW

SRT is ablative and works because normal tissues are avoided to the maximum extent possible. Prescriptions for SRT utilize fraction sizes greater than 6 to 8 Gy and higher total doses given over a brief period (less than 1 week). Treatments can be administered in 1 to 5 fractions. Additional technologies, including image guidance, robotic positioning tables, general anesthesia, rigid positioning devices, and highly conformal beam shaping technology, are required to deliver stereotactic treatments safely and with submillimeter accuracy (**FIGURE 4**).[1]

While conventional treatments exploit the differential radiosensitivity of normal tissues and tumors, SRT attempts to ablate the function of any living tissue where the beam is focused. Side effects from SRT are minimized by avoiding normal tissues as completely as possible. Irradiating wide areas of normal tissue or attempting to treat microscopic disease (i.e., a scar bed) is not possible with SRT, as irreversible side effects would be expected.

Intent

The intent of conventional radiotherapy (definitive or palliative) is most often distinguished by the prescription size (dose per fraction and total dose). The intent of SRT does not always fit neatly into the palliative or definitive categories. The cancer type and its radiosensitivity, the stage of disease, comorbidities, and the owner's goals distinguish the treatment intent of SRT.

The stage of the tumor as determined by the size of the mass is particularly important in setting expectations for owners as to the intent of SRT. In general, a small

tumor (less than 5 to 10 cm^3 in total volume) will receive a more uniform dose of radiation than a very large tumor and may be ablated to achieve durable remission with higher doses of radiation. Very large tumors cannot receive the entire intended prescription homogenously across their volume due to the proximity of adjacent normal tissues; thus, complete ablation of these tumors is not possible (**FIGURES 5 AND 6**). Nevertheless, these patients may still receive palliative benefit from SRT.

Side Effects

Due to the ablative nature of SRT, side effects may be acute or late. In contrast to conventional radiotherapy, rapidly proliferating normal tissues such as the skin are at risk for an irreversible late side effect when treating tumors with SRT (**FIGURE 7**).

FIGURE 7. Distal radius of osteosarcoma patient 6 months after completion of treatment with 10 Gy × 3 fractions of stereotactic radiation therapy. There is a necrotic, nonhealing ulcer present with exposure of underlying bone. This is an example of a late side effect occurring in a normal tissue (skin) typically associated with acute effects. Amputation was recommended.

It is important to emphasize to owners that most patients that undergo SRT are expected to experience minimal and reversible side effects if they are appropriate candidates and if proper planning and positioning are followed. Patient positioning and aiming of the radiotherapy beam must have submillimeter accuracy and precision for SRT to be successful and to minimize the probability of side effects.

RADIATION BIOLOGY

As discussed above, conventional radiotherapy and SRT exploit different aspects of tumor and normal tissue radiation biology. The mechanisms by which these different modalities work are described below.

Conventional Radiotherapy

Conventional radiotherapy seeks to exploit the differential radiosensitivity of normal tissues and tumors. The mechanism of conventional radiotherapy's action on normal tissues/tumors is described by the 5 Rs: repair, repopulation, redistribution, reoxygenation, and radiosensitivity.

Repair

Repair is defined as DNA double-strand break repair. Double-strand breaks to DNA are the main mechanism by which conventional radiotherapy damages both normal tissues and tumors. Tumors are inherently less able to repair DNA than normal tissues, and this differential repair capacity is exploited by the conventional radiotherapy treatment strategy, which gives normal tissues time to repair DNA damage between each fraction.

DNA damage in both normal tissues and tumors is detected within minutes to hours of a given dose of radiation, triggering the process of DNA repair. In normal tissues, this process is complete within 8 to 10 hours. If the interval between radiation fractions is too long, tumors can eventually repair DNA damage as well. This ability is why starting the first dose in a course of conventional radiotherapy on a Friday is generally discouraged, as the tumor will ultimately be able to repair the damage and the initial dose is thus "wasted" during the weekend break.[2]

Repopulation

Repopulation refers to the replication of a given tumor

or normal tissue cell after a fraction of radiation is administered. Between each fraction, normal tissue cells are given sufficient time to replenish their numbers. Repopulation is an important mechanism of normal tissue tolerance to radiotherapy, as both acutely responding normal tissues of self-renewal and late-responding normal tissues can sufficiently replenish their numbers between each fraction if given sufficient time.[2,3] However, in humans, head and neck squamous cell carcinomas exhibit a phenomenon called accelerated repopulation if the course of conventional radiotherapy takes longer than 6 weeks to deliver.[4] The extended duration of radiotherapy paradoxically induces the cancer cells to repopulate their numbers ever more rapidly as treatment progresses and results in treatment failure.[2]

Redistribution

Redistribution describes the growth kinetics of different cancer cells through the phases of the cell cycle. The G2 and M phases of the cell cycle are the most sensitive phases to radiotherapy-induced cell death. Fractionated radiotherapy exploits these sensitive phases of the cell cycle in 2 ways. First, multiple fractions of radiation given over time increase the probability of hitting a given cell when it is in the G2 or M phase. Second, fractionation alters the division kinetics of the cancer cells such that the cancer cells surviving after a given fraction are more synchronized in their cell cycles, increasing the chances that each subsequent radiotherapy fraction will hit them in the G2 or M phase.[5] Redistribution has minimal, if any, effect on normal tissues.[2]

Reoxygenation

Reoxygenation is the observation that, after a given fraction of radiotherapy, the tumor mass decreases in size, thus getting closer to a blood supply. This is important because tumors are composed of abnormal, torturous, and disorganized blood vessels with areas of significant hypoxia, and hypoxia is a driver of radiotherapy resistance. Normoxic cells are between 2.5 and 3.5 times more sensitive to cell death from a given dose of radiation than hypoxic cells.

Tumor tissues greater than 70 microns from a blood supply are prone to hypoxia, as this is the maximum distance oxygen can diffuse. As fractionated radiotherapy treatments kill part of the mass of a tumor at each fraction and the tumor begins to decrease in

Glossary

Ablation Complete removal of a tissue or its function.

Cell cycle Events that occur as part of cellular division. There are 4 phases of the cell cycle: G1, cell growth; S, DNA replication; G2, preparation for mitosis; M, mitosis. G0 is the phase of the cell cycle when cells are not actively dividing.

Conventional radiotherapy Radiation delivered with traditional fractionated techniques with either definitive or palliative intent.

Definitive Intent Radiotherapy delivered with the intent to achieve long-term durable remission of the disease. In some cases, cure is possible. Can be achieved using conventional techniques and multiple daily fractions to a high total dose or stereotactic radiotherapy.

Fraction A single radiotherapy treatment session.

Gray (Gy) Unit of radiation absorption, defined as 1 joule per kilogram of water.

Hypofractionation Large relative size in Grays. In veterinary medicine, normal fraction sizes for conventional definitive-intent treatment are between 2 and 3 Gy. Palliative treatments (fractions ≥4 Gy) and stereotactic treatments (fractions of 6 to >8 Gy) are examples of hypofractionation.

Growth kinetics Rate of cellular division of a population of cancer cells in a tumor. Tumors have a heterogenous population of cells that are in many different phases of cellular division at any given time.

Linear accelerator (LINAC) A medical device that generates high-energy electrons or photons for radiotherapy.

Palliative intent Radiotherapy delivered with the intent of shrinking or stabilizing the disease and minimizing the potential for treatment-related side effects, not achieving durable remission/survival or cure. Can be achieved using conventional or stereotactic techniques. Doses are typically hypofractionated to minimize the duration of treatment and avoid side effects.

Stereotactic radiotherapy Ablative radiotherapy treatment technique that uses image guidance and rigid immobilization to deliver the dose of radiation to the tumor while minimally affecting normal tissues. Synonyms include SABR (stereotactic ablative radiotherapy), SBRT (stereotactic body radiotherapy), and SRS (stereotactic radiosurgery). SRS is delivered in a single fraction while the other techniques are typically delivered in 1 to 5 fractions.

Stereotactic radiosurgery is a form of SRT; its name comes from the fact that it is given in only 1 dose.[10]

size, the resultant proximity to a blood supply creates a more normoxic tumor microenvironment, thus reoxygenating and further sensitizing the tumor to additional fractions of radiotherapy. Reoxygenation has minimal to no effect on normal tissues.[2]

Radiosensitivity

Radiosensitivity is the inherent sensitivity of a tumor to a given fraction of radiation. In veterinary medicine, cancers including melanoma and lymphoma are known from in vitro experiments with canine-derived cell lines, as well as clinical experience, to have high inherent radiosensitivity.[6] Conversely, clinical experience with feline oral squamous cell carcinoma reveals this tumor type to be poorly sensitive to radiotherapy.[7]

Stereotactic Radiotherapy

The radiation biology of normal tissues and tumor cells in response to ablative doses of SRT may differ from the radiation biology of conventional treatments. Several aspects of the 5 Rs are thought to also be important drivers of tumor response to treatment, especially reoxygenation and radiosensitivity.

Vascular endothelial cell death is a significant factor in the observed responses of tumors to SRT. After the tumor vascular endothelium is destroyed, the tumor mass is deprived of a blood supply and shrinkage/response is observed.[8,9] The vascular endothelial response to very high doses of radiation is, in fact, what led to the invention of SRT delivery equipment. The gamma knife, invented in the 1950s to treat cerebral arteriovenous malformations in humans, is still in use for this indication today as well as for the treatment of metastatic/primary brain tumors using stereotactic radiosurgery. Stereotactic radiosurgery is a form of SRT; its name comes from the fact that it is given in only 1 dose.[10]

Immunomodulation is another mechanism by which tumor cell death could be induced by SRT. Because a given dose of SRT is highly toxic to any living cell, the immediate die-off of large portions of the tumor mass releases antigens. The massive amount of antigen release may stimulate the immune system to recognize the tumor as non-self and break immunotolerance.[11] This is highlighted by the occasional observation of the abscopal effect after radiotherapy in humans. The abscopal effect is the regression of metastatic lesions following treatment of the primary tumor with radiotherapy. The abscopal effect is thought to be more likely to occur with SRT but has also been observed in conventional radiotherapy.[12]

Repopulation and reoxygenation as described for conventional radiotherapy may also be important players in observed tumor response to, and normal tissue sparing in, SRT. In preclinical models, as well as in humans, the reoxygenation effect has been observed in response to SRT.[13] Additionally, there is some clinical evidence that fractionated rather than single doses of SRT may be safer/more effective in humans with lung tumors.[14]

KEY POINTS

SRT is a powerful treatment technique for patients with cancer located anywhere in the body. When evaluating clinical cases that might benefit from SRT, clinicians should remember:

- Gross disease must be present to avoid normal tissue toxicity and appropriately target the lesion.
- Nasal and brain tumors are typical candidates for SRT, with some of the most mature data and publications supporting its use.
- Image guidance and robotic positioning technologies allow SRT for tumors in virtually any anatomic location.
- If careful attention is paid to the technical aspects of setting up the patient and the correct cases are selected, any potential side effects of SRT are expected to be minimal. If side effects occur, the vast majority are expected to be reversible, acute side effects.
- Late side effects from SRT may occur in tissues more typically associated with acute side effects, such as the skin or oral mucosa. Late side effects manifesting in the skin, including nonhealing/necrotic ulcers, may be of high consequence to patient quality of life. Care must be taken in patient selection, treatment planning, and radiation delivery to avoid such late effects.

■ SRT does not completely replace the role of conventional radiotherapy. TVP

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CONTINUING EDUCATION

Conventional Versus Stereotactic Radiotherapy

TOPIC OVERVIEW

This article describes basic concepts of the process of radiotherapy in veterinary oncology and radiation biology for veterinarians in general practice.

LEARNING OBJECTIVES

Readers will be able to describe the use of conventional and stereotactic radiotherapy for definitive or palliative treatment and identify patients that might benefit from these therapies.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment when approval has been received. To receive credit, take the test for free by visiting **vetfolio.com** and entering the title of the article in the search bar. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

1. **The 5 Rs of radiotherapy are repair, repopulation, redistribution, reoxygenation, and radiosensitivity.**
   a. True
   b. False

2. **The difference between the intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) radiotherapy administration techniques is:**
   a. In VMAT, the gantry rotates dynamically while the position of the gantry in IMRT treatments is fixed.
   b. In IMRT the gantry rotates dynamically while the position of the gantry in VMAT treatments is fixed.

c. IMRT consistently results in faster delivery times than VMAT.
d. IMRT only produces rectangular dose shapes.

3. **What is the difference between definitive-intent radiotherapy treatment and palliative-intent radiotherapy treatment?**
   a. Definitive-intent treatment aims to provide approximately 6 months of disease control, while palliative-intent treatment aims to provide approximately 2 to 3 months of disease control.
   b. Palliative-intent treatment results in only minimal side effects.
   c. Definitive-intent treatment always results in severe side effects.
   d. Definitive-intent treatment aims to provide a durable remission or cure while palliative-intent treatment aims to alleviate pain and discomfort while minimizing side effects.

4. **Which of the following statements are true with regard to stereotactic radiotherapy (SRT)?**
   a. Submillimeter accuracy and precision in dose administration are required to deliver SRT safely.
   b. Cone beam computed tomography and robotic positioning tables are technologies used to help administer SRT.
   c. Rigid positional devices are used to reproduce patient position.
   d. All of the above

5. **Stereotactic radiotherapy can be delivered with either definitive or palliative intent.**
   a. True
   b. False

6. **Which of the following cell cycles is most sensitive to radiotherapy?**
   a. G0
   b. S
   c. G2 and M
   d. G1

7. **Which of the following statements regarding reoxygenation is true?**
   a. Normal tissues are extremely sensitive to reoxygenation.
   b. Normoxic cells are between 2.5 and 3.5 times more sensitive to cell death from a given dose of radiation than hypoxic cells.
   c. Tumors have similar blood vessels to normal tissues.
   d. None of the above

8. **Which of the following statements regarding radiosensitivity is true?**
   a. Radiosensitivity is the inherent sensitivity of a tumor to a given fraction (dose) of radiation.
   b. No in vitro studies of the radiosensitivity of veterinary cancers have been performed.
   c. Feline oral squamous cell carcinoma is the most sensitive tumor type to radiotherapy.
   d. Lymphoma is the tumor type that is least sensitive to radiotherapy.

9. **Acute radiation side effects are defined as:**
   a. Irreversible effects that occur in rapidly proliferating normal tissues such as skin, oral mucosa, and gastrointestinal mucosa.
   b. Typically reversible effects that occur in rapidly proliferating normal tissues such as skin, oral mucosa, and gastrointestinal mucosa.
   c. Irreversible effects that occur in slowly proliferating normal tissues such as bone, nervous system, and muscle.
   d. Typically reversible effects that occur in slowly proliferating normal tissues such as bone, nervous system, and muscle.

10. **Late radiation side effects are defined as:**
    a. Irreversible effects that occur in rapidly proliferating normal tissues such as skin, oral mucosa, and gastrointestinal mucosa.
    b. Typically irreversible effects that occur in slowly proliferating normal tissues such as bone, nervous system, and muscle.
    c. Typically reversible effects that occur in slowly proliferating normal tissues such as bone, nervous system, and muscle.
    d. Effects that occur in the central nervous system.