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Radiation Therapy (26-Mar-2003)

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Introduction

Radiation therapy for tumors of the central nervous system in dogs and cats is a viable treatment option. The availability of radiotherapy has increased with the advent of the veterinary specialty of radiation oncology, resident training programs in this specialty, and University and referral practices offering this treatment modality. Veterinary patients may not be cured of their disease, but will have an increased length and quality of life.

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Principles of Radiation Therapy

Process of Radiotherapy - Radiotherapy is a clinical treatment modality where ionizing radiation is used to treat patients with malignant neoplasms. The goal of radiation therapy is to deliver a measured dose of radiation to a defined volume with minimal damage to surrounding normal tissue, resulting in eradication of the tumor. Radiotherapy is generally given in divided doses or fractionated. Radiotherapy is useful in the treatment of localized tumors and can provide long-term local control with preservation of regional function. There are several principles that dictate the prescription of irradiation and therefore the management of cancer patients.

- Tumor staging. Complete evaluation of the full extent of the tumor, which may include multiple imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and radiography
- Knowledge of the biologic behavior of specific tumor types. This includes potential areas of metastasis that may dictate elective irradiation of lymphatics.
- Defining the goal of therapy: Curative versus palliative treatment.
 - Curative, it is projected that the patient has the probability for long-term survival.
 - Palliative, patient survival for an extended period is not projected. However, irradiation of the tumor will improve the patient's quality of life.
- Selecting an appropriate treatment course, which may include irradiation alone or in combination with surgery and or chemotherapy.
- Determination of the irradiation dose and volume to be treated. This depends upon the anatomic location, histological type, tumor stage, potential lymph node involvement, other tumor characteristics and normal structures present in the area to be irradiated.
- Evaluation of the patient's general condition.

Radiation Doses and Volumes - Different doses of radiation are needed for tumor control, depending on the type and initial number of clonogenic cells present. Clonogenic cells are capable of producing a copy or clone. If these cells are malignant a tumor is generated or regenerated. For example, larger doses are needed to eradicate a 2 cm tumor volume as compared to microscopic disease that may be present after incomplete surgical resection. A clinical tumor can comprise several compartments: macroscopic (visible or palpable), micro-extensions into adjacent tissues, and subclinical disease which is presumed to be present, but not detectable. Radiotherapy treatment portals must adequately encompass all three compartments plus a margin to compensate for geometric inaccuracies during the treatment period. Geometric inaccuracies are divided into inherent mechanical imprecision in the treatment machine and those related to defining the target. The latter includes target determination, target localization and reproducibility of patient positioning at each treatment.

Defined volumes in radiotherapy treatment planning include the gross tumor volume (GTV), the clinical target volume (CTV), and the planning target volume (PTV) [1]. The GTV is defined as all known gross disease including affected lymph nodes. The CTV includes the GTV plus a margin for suspected microscopic tumor extension. The PTV provides a margin around the CTV to compensate for variation in daily treatment set-up or other anatomic movement such as breathing.

Radiation doses are measured in units of absorbed dose, Gray (Gy). A Gray is equal to 1 J/kg energy absorbed in tissue. In general, radiation doses are given in daily, smaller fractions (Monday through Friday) to achieve the desired total dose over several weeks. Examples of fractionation schemes in veterinary radiation oncology include daily 3 - 3.2 Gy fractions for 15 - 16 treatments for a total dose of 48 Gy and 2.5 Gy daily fractions for 18 treatments for a total dose 45 Gy.

Radiobiology

Radiation Damage and Cell Kill - Ionizing radiation kills cells by interacting with critical cellular molecules, such as deoxyribonucleic acid (DNA). The interaction of ionizing radiation with the molecular infrastructure of the cell results in chemical reactions. Damage to the DNA is either direct (DNA strand cleavage) or indirect, mediated by free radicals. Most cells die a reproductive death after irradiation and will therefore die at a rate consistent with the cell cycle duration. Slowly proliferating tissues respond slowly, whereas rapidly proliferating tissues and most tumors respond more quickly. There are many factors that influence the radiation response of cells in normal tissues and tumors. Some important factors that account for radioresponsiveness are the number of clonogenic cells, redistribution or reassortment of cells in the cell cycle, repair of radiation injury, repopulation by stem cells, and the oxygenation status.

Proliferating cells are more radiosensitive and have a greater cell loss/turnover rate. Normal tissues and tumors that are rapidly proliferating are more likely to be irradiated at the radiosensitive phase of the cell cycle. Cells are most sensitive to ionizing radiation during M (mitosis) and G2 phases of the cell cycle and most resistant in late S phase (DNA synthesis). The redistribution or reassortment of cells in the cell cycle is one reason behind fractionation of the radiotherapy dose. Dividing the radiation dose into multiple fractions allows cells to reassort to more sensitive phases of the cell cycle before the next treatment.

Almost all tumor cell lines undergo some repair of sublethal and potentially lethal radiation damage [2]. Repair of radiation damage will decrease tumor control, but increases normal tissue tolerance. Hence, another reason the radiation dose is fractionated is because normal tissues are included in the radiotherapy field. Cells of normal tissues are killed by ionizing radiation and time needs to be allotted for their repair and repopulation. Repopulation of stem cells will decrease tumor control, but increases normal tissue tolerance.

The oxygen status of the tissue undergoing irradiation affects radiosensitivity. The presence of oxygen is necessary to fix or make permanent DNA damage mediated by free radicals. When oxygen is absent, three times as much radiation is required to produce the same effect as when tissues are fully oxygenated [3]. Many tumors are known to contain foci of cells that are hypoxic because of their distance from capillaries. During the course of radiation treatment oxygenated cells close to capillaries may be killed, allowing oxygen to reach previously hypoxic cells (reoxygenation), thereby increasing their radiosensitivity [3]. Less responsive tumors are thought to have a high percentage of hypoxic cells or a lower rate of reoxygenation [4].

Normal Tissue and Tumor Response to Radiation - After clinical doses of ionizing radiation, cell death typically occurs at the next attempt of mitotic division [5,6]. Therefore, the time to development of most normal tissue injury depends on the cell turnover rate of the tissue in question. Acute responses to radiation are seen in tissues with a high rate of cell turnover. Examples include gastrointestinal mucosa, bone marrow, skin, oropharyngeal and esophageal mucosa. Hierarchical cell populations exist in these tissues consisting of stem cells, progenitor cells, and highly differentiated mature functional cells

[7]. Ionizing radiation depletes the stem and progenitor cell pools. Function is maintained until the differentiated cell pool is depleted due to normal cell loss and will not be restored until the stem and progenitor cell pools are replenished. Late effects of radiation therapy can be considered as secondary to depletion of slowly proliferating cells. Examples of tissues with a slow rate of cell loss include nervous tissue, kidneys, blood vessels, fibroblasts in the dermis and bones. In contrast to acutely responding tissues, slowly proliferating tissues have both functional and proliferating roles; they are considered flexible rather than hierarchical [7]. Late effects are much more dependent on the dose size and the time since exposure to radiation. Acute effects are relatively independent of dose and determined more by the normal and rapid rate of differentiated cell loss [8]. In general, most tumors respond to radiation like acutely responding tissues.

Tissue repair of radiation injury can occur when a dose of radiation is fractionated into several smaller doses rather than delivered in one large dose. Fractionation of radiation doses will spare slowly responding normal tissues and works to a slight disadvantage for tumor control. Slowly responding tissues have a greater capacity for tissue repair than rapidly responding tissue and fortunately most tumors are rapidly responding. Tissue repair and the sparing of slowly responding normal tissues is the reason that most radiation therapy is delivered in multiple small fractions over 3 to 6 weeks.

Technology and Equipment

Treatment of tumors with radiotherapy involves the use of external beam radiotherapy machines or brachytherapy. Brachytherapy involves the placement of sealed radioactive sources into or directly adjacent to the tumor. External beam radiotherapy machines include orthovoltage units, linear accelerators, and machines using isotopes.

Brachytherapy - An advantage of brachytherapy is that high doses can be delivered locally to the tumor in a short period of time with low doses in the surrounding normal tissue. Isotopes used in brachytherapy can be embedded in a surface applicator, which is directly placed on the tumor. Surface applicators are used for superficial tumors; the maximum dose is at the surface and falls off rapidly with depth. Isotopes can be sealed into seeds, needles or tubes that are placed into body cavities (intracavitary), tubular organs (intraluminal), or directly through the tumor (interstitial). With all of these methods the radioactivity is sealed inside a shell to prevent leakage of radioactivity into tissues. Today the most commonly used isotope is Iridium-192, which emits gamma radiation with an average energy of 0.380 million-electron volts (MeV). Isotopes used in brachytherapy are implanted in the patient for a limited period of time until the desired dose is delivered and then removed.

Orthovoltage units - Orthovoltage units are relatively low energy external beam radiotherapy machines, x-ray machines operating in the range of 150 - 500 kilovolts peak (kVp). In a typical orthovoltage beam, the maximum dose is at the skin surface and falls to 90% at approximately 2 cm of depth. Due to this dose drop off, it is difficult to treat deeply seated tumors without causing severe skin reactions.

Linear Accelerators - Linear accelerators are external beam radiotherapy machines that use high-frequency electromagnetic waves to accelerate electrons to high energies. The electrons can be extracted to treat superficial tumors or directed to strike a target to produce high-energy x-rays used to treat deep-seated tumors. There is increased flexibility with linear accelerators where lower energy electrons can be used to treat superficial skin tumors and higher energy x-rays used to treat deeper tumors with a lower dose to the skin.

External Beam Radiotherapy Machines using Isotopes - External beam radiotherapy machines using isotopes include cobalt-60 (Fig. 1) and cesium-137. Because isotope machines are constantly emitting radiation they need to be shielded when in the "off" position. When the machine is in the "on" position, the isotope source is moved to an unshielded window allowing the radiation to be directed at the patient. The cobalt-60 source decays over time with a half-life of 5.26 years, emitting gamma radiation with an average energy of 1.2 MeV. Like the higher energy x-ray beam from a linear accelerator there is also a skin sparing benefit with cobalt-60 treatment; the maximum dose is beneath the skin surface. The relatively high penetrability of cobalt-60 makes it a good isotope for teletherapy. In contrast, cesium-137 has lower gamma ray energy of 0.662 MeV and few cesium machines are still in use.



Figure 1. Isocentric Cobalt-60 external beam radiotherapy therapy machine. The letter "A" is located on the source head. This houses the radioactive source, which is shielded in the "off" position and moved to an unshielded opening in the "on" position for patient irradiation. - To view this image in full size go to the IVIS website at www.ivis.org . -

Advanced Technology - Advances in machinery and computers have resulted in more precise treatments, targeting the tumor volume and reducing dose to normal tissues. The development of intensity-modulated radiotherapy (IMRT) through the application of 3D treatment planning and multileaf collimators (MLCs) has achieved this goal of improving the therapeutic ratio. IMRT is a 3D conformal radiotherapy technique where treatment beams are spatially and temporally modulated to maximize dose to the tumor volume, while minimizing dose to normal structures. Newer linear accelerators permit more control over the shape of the treatment beam with the use of a MLC, which allows shaping of the treatment field to conform to the contour of the tumor. The MLC has 20 to 80 movable leaves, or shields, that can block some fraction of the radiation beam and allow shaping of the field [9]. This has led to the development of helical tomotherapy, which is the combination of a linear accelerator with a MLC and a helical CT gantry (Fig. 2). The integration of CT capabilities and IMRT into one unit makes tomotherapy a closed loop for planning, delivery and verification in radiotherapy [10]. The first clinical tomotherapy unit has been installed at the University of Wisconsin and is undergoing testing. Dogs with spontaneously arising nasal tumors will be the first patients treated on this unit and the conformal avoidance capabilities of helical tomotherapy will be investigated. With this new technology the nasal tumor can be effectively treated while avoiding excessive dosage to the eyes. The goal in treatment advancements is to effectively and accurately treat the tumor while minimizing radiation effects on surrounding normal tissues, thus improving the therapeutic ratio.



Figure 2. Tomotherapy Unit. This radiotherapy unit combines a 6 MV linear accelerator with a helical CT gantry. This combination of technologies provides accurate treatment set-up verification with on-line imaging, and dose delivery verification during treatment. (Courtesy of TomoTherapy, Inc., Madison, WI, USA). - To view this image in full size go to the IVIS website at www.ivis.org . -

Another highly technical treatment is stereotactic radiotherapy. This involves focal irradiation using high doses to stereotactically localized lesions. The requirements for positional accuracy of radiation dose delivery are even more rigorous in stereotactic irradiation than in standard radiotherapy because high doses are given to small lesions in proximity to vital radiosensitive structures [11]. Stereotactic irradiation techniques are most often applied to intracranial structures since the cranium lends itself to the stable fixation of stereotactic frames rigidly attached to the patient. These stereotactic frames allow accurate determination of spatial coordinates of any point within the organ. These coordinates are used to direct external beam radiation to the target volume [11]. Although most veterinary patients are treated with external beam radiation using either a linear accelerator or Cobalt-60 unit, the veterinary radiation oncology community is maintaining a progressive profile. In a recently reported study of radiosurgery using a stereotactic headframe system to irradiate 3 dogs with brain tumors, survival times were 56, 66 and 227 weeks [12]. Using a stereotactic headframe and CT localization the brain tumors were targeted with non-coplanar stereotactically focused beams of radiation in a series of arcs to deliver a single dose of 10 - 15 Gy with great accuracy [12].

Stereotactic irradiation, IMRT techniques and other innovative advances in radiotherapy such as tomotherapy are highly computer driven and require a large number of personnel for treatment planning and delivery. Therefore, these techniques are limited to institutions that employ medical physicists, dosimetrists (involved in radiation computer treatment planning) and computer personnel in addition to radiation oncologists and radiation therapy technologists.

Radiotherapy of the Central Nervous System

Neural Cell Response to Radiation - Normal cells in the brain and spinal cord are either static or slowly dividing. Because of this, radiation effects on brain tissue are primarily delayed reactions with little dose-limiting acute toxicity other than edema. Because the central nervous system (CNS) is a late-reacting tissue, normal CNS parenchyma is sensitive to the size of individual radiation doses (dose per fraction). There is a large capacity for sublethal and potentially lethal damage repair of neural tissue at lower doses per fraction. Tumor cells have diminished capacity for sublethal damage repair; therefore, there is less sparing of tumor cells as compared to normal neural tissue with smaller fraction sizes. A large percentage of tumor cells are actively dividing and will reassort into radiosensitive phases of the cell cycle between daily fractions of radiation, thus further increasing the therapeutic differential.

Radiotherapy Protocols - In human medicine, primary CNS tumors are treated with external beam radiotherapy to a total dose of 50 to 60 Gy in 25 to 30 fractions delivered over 5 to 6 weeks [13]. Due to the difficulties involved with required daily anesthesia and increased cost, most veterinary patients are treated with a lower total dose and fewer fractions. Treatment regimens for CNS irradiation reported in the veterinary literature vary from total doses of 30 - 54 Gy in 2.4 - 9 Gy fractions

[14-26,52,53]. Due to the fact that neural tissue is late-responding in terms of radiation effects, multiple fractions of 3 Gy or less should be used. With this fractionation schedule, the tolerance dose of normal CNS tissue is 50 - 55 Gy [27]. At the University of Wisconsin, School of Veterinary Medicine the neural tissue protocol is 45 Gy given in 18, 2.5 Gy fractions Monday through Friday over a 4-week period.

Radiotherapy of Brain Lesions

Basic Principles and Techniques - Delivery of radiotherapy to the brain can be accomplished with fractionated external beam irradiation, stereotactic irradiation, and interstitial implantation of radioactive sources. In veterinary medicine, radiotherapy is used to treat tumors and non-neoplastic processes and is generally delivered by fractionated external beam irradiation. Megavoltage (Cobalt-60, linear accelerator) irradiation is preferred over orthovoltage radiation as the latter has poor beam penetration, inconsistent energy absorption, and limited radiation portal configuration. Computer based radiation treatment plans are preferred allowing accurate targeting of the intracranial lesion and improved target dose distribution. Intracranial masses in dogs and cats most often have presumptive diagnoses based on the computed tomographic (CT) and magnetic resonance (MR) characteristics [28-30]. Histopathologic diagnosis is often not pursued prior to treatment with radiation therapy and a presumptive neoplastic classification is based on mass location and contrast enhancement on CT or MR imaging (see Brain tumors). Masses in a peripheral location with marked contrast enhancement are considered meningiomas, intra-axial location with poor or heterogeneous contrast enhancement are consistent with tumors of glial origin, contrast enhancing masses at the level of the sella turcica are deemed pituitary tumors, and enhancing masses of choroid plexus location are regarded as choroid plexus tumors [25,28-30].

Radiotherapy of Brain Tumors - In the few reports in the literature of veterinary patients with intracranial lesions treated with radiotherapy, it has been shown to be an effective treatment [14-17,20,22,24,25,31,52,53]. Reported median survival times in dogs with brain tumors following radiation therapy alone range from 150 - 360 days [14,16,17,23,25,31] and is better for dogs with pituitary tumors and mild neurologic signs [15,22]. Table 1 and Table 2 summarize the reports in the veterinary literature of radiation therapy for intracranial masses and pituitary tumors. Patient numbers in these studies are small, making it difficult to determine the radioresponsiveness of particular tumor types. The most common intracranial tumors in dogs are meningiomas and gliomas (astrocytoma, oligodendroglioma); meningiomas are the most common tumors in cats [27] (see Neoplasia of the nervous system). Generally, intracranial tumors do not metastasize and local control is beneficial [27].

Table 1. Summary of reports of radiation therapy for dogs with intracranial masses.					
Authors	No. Dogs	Radiation Source *	Total Dose	Protocol **	Median Survival (wks)
Turrel, et al.	4	Cobalt-60	36 Gy	6 Gy x 6 fx	46
Heidner, et al.	25	Cobalt-60	45.6 - 48 Gy	3.8 - 4 Gy x 12 fx	20
Evans, et al.	9 5	240 kV 240 kV	39 Gy 45 Gy	3.25 - 3.75 Gy x 12 fx	19 32
Norman, et al.	47 26	Modified CT-140 kV	Median-34 Gy Median-39 Gy	5.6 Gy x 1 - 15 fx	19 32
Spugini, et al.	29	Cobalt-60	48 - 54 Gy	3 Gy x 16 fx	35.7
Brearly, et al.	83	4 MV linac	38 Gy	Wkly fx 5,7,8,9,9 Gy	43.7
Theon, et al.	20	Cobalt-60	48 Gy	4 Gy x 12 fx All post-surgery	Not reported ‡PFS= 120±36
Axlund, et al.	12	Cobalt-60 6 MV Linac	28 - 49.5 Gy	Not reported All post-surgery	66

*Radiation sources are external beam and include megavoltage machines, Cobalt-60 and linear accelerators (linac) and lower energy machines, orthovoltage (250 kV) and a modified CT scanner (modified CT-140 kV).

**Radiation protocols are described in terms of dose per fraction (Gy) times the total number of fractions (fx) given.

‡PSF refers to the median (± SE) duration of progression free survival in weeks.

Table 2. Summary of Reports of Radiation Therapy for Dogs with Pituitary Tumors.					
Authors	No. Dogs	Radiation Source *	Total Dose	Protocol **	Median Survival (wks)
Dow, et al.	7	6 MV linac	40 Gy	4 Gy x 10 fx	106
Mauldin, et al.	10	Cobalt-60	54 Gy	3 Gy x 18 fx	10
Theon, et al.	24	Cobalt-60	48 Gy	4 Gy x 12 fx	46.8 +/- 23.6

*Radiation sources are external beam megavoltage machines, Cobalt-60 and linear accelerators (linac).

**Radiation protocols are described in terms of dose per fraction (Gy) times the total number of fractions (fx) given.

In one study using 250 kV orthovoltage irradiation, 14 dogs with intracranial masses received either 39 or 45 Gy over 25 to 41 days. These dogs receiving radiation therapy had better survival rates than dogs reported in the literature that received no treatment (mean and median of 345 and 489 days versus 30 and 81 days). Dogs receiving 45 Gy did better than those receiving 39 Gy with a median survival of 519 days and 153 days, respectively [17]. Another study of 4 dogs reported a mean survival time of 322 days in dogs with intracranial tumors receiving 30 to 36 Gy of external beam radiation [14]. A larger, retrospective study of 86 dogs with brain tumors found that dogs that were treated with external beam radiation lived significantly longer than dogs treated with surgery or symptomatic treatment [16]. In this same study, it was found that dogs with mild or moderate initial neurologic dysfunction had a better prognosis than dogs with severe initial neurologic impairment [16]. A recent retrospective study of 29 dogs with intracranial masses treated with radiation therapy alone reported a median survival of 250 days [25]. Cobalt-60 radiation was delivered in 3 Gy fractions on a daily, Monday through Friday basis for a total of 48 Gy in 28/29 dogs and meningioma was the presumptive diagnosis in 22/29 dogs [25]. A less intensive radiotherapy protocol has been advocated by one group [23]. This retrospective analysis of 83 dogs with intracranial masses treated with a hypofractionated radiotherapy protocol reported a median survival of 43.7 weeks. Late radiation toxicity was suspected as the cause of death or euthanasia in 12 dogs by the authors; the radiotherapy protocol was escalating weekly doses of 5, 7, 8, 9, 9 Gy [23]. The large fraction size used to irradiate late responding tissue (brain) would be expected to result in signs of late radiation toxicity.

Radiation therapy is a useful adjuvant therapy to surgery [24,32,52]. Twenty dogs with incompletely resected meningiomas treated with external beam radiotherapy had median progression-free survival rates of 30 ± 9 months [24]. In this same study, immunostaining of the tumors detected progesterone receptors in 14/20 dogs, suggesting a potential role for hormonal therapy in canine meningioma [24]. A more recent study compared surgery alone or surgery followed by radiation therapy for the treatment of intracranial meningiomas [52]. Twenty-six dogs were included in this study; 14 treated with surgery alone and 12 treated with surgery and adjuvant radiotherapy. Median survival times were significantly better for dogs treated with surgery followed by radiation therapy (16.5 months) as compared to surgery alone (7 months) [52].

Canine pituitary tumors respond to external beam radiotherapy [15,21,22]. The space occupying affect of pituitary macrotumors can cause neurologic signs [15,22]. Unlike the human counterpart, canine pituitary tumors are less amenable to surgical excision due to pituitary gland anatomy and tumor extension into the hypothalamus [33]. Radiation therapy is an effective treatment for these tumors to alleviate neurologic symptoms. Radiation therapy has resulted in a reduction in tumor size in both endocrine-inactive and functional pituitary tumors [15,20-22]. Response of functional pituitary macroadenomas and macroadenocarcinomas to radiation alone or radiation and mitotane therapy was evaluated in 6 dogs prospectively with a reported mean and median survival of 740 and 743 days. All dogs had a reduction in tumor size and resolution of neurological deficits [15]. A more recent study of 24 dogs with pituitary macrotumors reported a significant correlation between relative tumor size and severity of neurological signs and between relative tumor size and remission of neurological signs after irradiation [22]. This study reported a median overall survival rate of 11.7 ± 5.9 months, [22] supporting the efficacy of radiotherapy for pituitary macrotumors. However, in a report of 6 dogs with pituitary-dependant hyperadrenocorticism (PDH) (with detectable pituitary tumors but without neurologic abnormalities) treated with external beam radiotherapy, there was inadequate control of clinical signs of PDH in 5/6 dogs [21]. Tumor size decreased in all dogs and was no longer visible in 4 [21]. Dogs with significant neurologic signs and larger tumors have a poorer prognosis [22]. Radiation therapy may be indicated in cases of PDH with macrotumors to reduce or eliminate these masses before neurologic signs become evident. Radiation therapy was also used to treat 3 cats with acromegaly and insulin-resistance diabetes mellitus with a mass in the area of the pituitary gland identified on CT. After completion of radiotherapy, insulin

requirements were decreased in all cats, although transient in one. Diabetes mellitus resolved in 2 cats [20]. A more recent report describes the use of radiotherapy in the treatment of pituitary tumors in 5 cats [53]. In this study diagnosis was based on either CT or MR imaging. A mean total dose of 39 Gy was delivered on a Monday, Wednesday, Friday schedule with median survival times of 15 months, (range 5.5 - 20.5 months) [53]. The 3 cats presenting with neurologic signs showed marked improvement during and/or after the course of radiotherapy and one of two cats with diabetes mellitus and acromegaly had a significant reduction in insulin requirements [53].

Radiation Therapy for Granulomatous Meningoencephalomyelitis - Radiotherapy is advocated for treatment of granulomatous meningoencephalomyelitis (GME) in dogs [19]. GME is an idiopathic, inflammatory disease of the CNS in dogs, characterized by large perivascular accumulations of mononuclear cells in the parenchyma and meninges [34]. Radiation is proposed as a treatment for GME on the basis that GME may represent primary B-cell lymphoma [35]. In a retrospective study of 42 dogs with histologic confirmation of GME, a significant increase in survival was seen in dogs that received radiation [19]. Necropsy findings in 3 dogs that received radiation had no evidence of GME in irradiated areas of the brain, suggesting treatment efficacy [19].

Radiotherapy of Spinal Cord and Peripheral Nerves

Basic Principles and Techniques - Tumors of the spinal canal can be either intramedullary, intradural-extramedullary or extradural in location. Tumor types include meningioma, neuroepithelioma, ependymoma and nerve sheath tumors; osteosarcoma is the most common extradural tumor (see Spinal cord tumors). Myelography is usually performed when a spinal cord mass is suspected, but CT and MRI scanning provide additional information. In human medicine, MRI has replaced myelography and CT as the imaging study of choice for evaluation of tumors of the spinal canal [36].

Generally, parallel-opposed lateral portals are used to treat spinal cord tumors in companion animals (Fig. 3). Treatment field borders should encompass two vertebral bodies above and below the tumor as defined by myelography to avoid marginal miss. Treatment plans can be one-dimensional (manual calculation of dose at a weighting point) or computer based. Portal localization radiographs should be taken at initiation of treatment to verify radiation treatment field.



Figure 3. Photograph of a radiation treatment set-up using Cobalt-60 in a dog with an incompletely resected nerve sheath tumor located at the level of the cranial lumbar vertebrae. The patient is treated with parallel opposed lateral fields with the dose centered at mid-body. Skin markings are made to facilitate daily treatment set-up. - To view this image in full size go to the IVIS website at www.ivis.org . -

Vertebral and Spinal Cord Tumors - Radiation therapy has been used postoperatively in the treatment of spinal cord tumors in human and veterinary medicine [26,36,37]. The same radiobiological considerations and treatment protocols discussed earlier in the brain section hold true for the spinal cord. Radiotherapy of spinal cord tumors is indicated in the post-operative setting after decompression laminectomy of the primary lesion. In a study of dogs treated either with radiotherapy and chemotherapy (n = 6) or surgery, radiotherapy and chemotherapy (n = 8) for primary and metastatic osteosarcoma and primary fibrosarcoma vertebral tumors in dogs the median survival time was 150 days [37]. This was not significantly different than median survival times for dogs treated with surgery or surgery and chemotherapy (n = 6) [37]. A study of 9 dogs with spinal cord tumors irradiated after decompressive surgery reported a median survival time of 17 months [26]. The majority of tumors in this study were meningiomas [26]. In a study of 22 dogs with spinal tumor treated with surgery alone, the median survival time was 240 days [38]. Although it is a relatively small study, it appears that adding radiotherapy to surgery for spinal cord tumors increases survival as compared to surgery alone [26].

Malignant Peripheral Nerve Sheath Tumors - Malignant peripheral nerve sheath tumors (MPNST) (see Peripheral nerve tumors) are amenable to postoperative radiotherapy. Computer based treatment planning is preferred using CT examinations obtained post surgery. Six dogs treated at the University of Wisconsin, School of Veterinary Medicine with MPNST in the post-operative setting had a median survival time of 448 days.

Lymphoma - In terms of radiosensitivity, lymphoma responds rapidly to lower doses of radiation as compared to other tumors. This is because lymphocytes die an intermitotic, early death due to apoptosis. Apoptosis is programmed cell death, which is characterized by a stereotyped sequence of morphologic events [39]. Radiation-induced cell death via apoptosis is highly cell-type dependent in which hemopoietic and lymphoid cells are prone to rapid cell death by the apoptotic pathway [39]. Unfortunately, lymphoma is often a multisystemic disease and rarely localized [40], therefore radiotherapy is not an

optimal treatment modality. Whole body irradiation is fraught with normal tissue complications, both acute and late effects [41]. Localized radiotherapy for dogs and cats with spinal lymphoma in the postoperative setting can provide clinical improvement, but does not address the systemic nature of the disease or the propensity for positive titer for feline leukemia virus in cats [40,42,43]. Craniospinal radiotherapy where the entire neuroaxis (brain and spinal cord) is irradiated has been reported in combination with chemotherapy in the treatment of CNS lymphoma in dogs [42]. In this study a marked response was reported in 4 dogs treated with a combination of systemic chemotherapy, intrathecal chemotherapy and craniospinal irradiation, however, the effect was not durable [42].

Chemotherapy

Chemotherapy has been reported sporadically in combination treatment with radiotherapy of CNS tumors [16,42]. In human medicine chemotherapy is used as an adjuvant to irradiation or surgery for intracranial tumors [13]. The blood-brain barrier limits delivery of chemotherapeutic drugs. Drugs with lipid solubility such as nitrosoureas, vincristine, cisplatin and procarbazine may reach therapeutic levels with the CNS [13]. Intrathecal injection of chemotherapeutic agents into the CSF space has been used, but only a limited number of agents are suitable. These include thiotepa, methotrexate, and cytosine arabinoside [13].

Chemotherapy has been used in combination in a small number of dogs with spinal cord tumors [37,38]. In these studies the addition of chemotherapy had no significant impact on overall survival.

Sequelae of Treatment

Acute Toxicity of the Brain - Although relatively uncommon, acute toxicity secondary to radiation therapy of the CNS can occur. This is manifested by a transient worsening of clinical signs occurring early in the treatment course and is a result of peritumoral edema [13]. Patients usually respond to a short course of corticosteroids. Persistent or refractory clinical signs may indicate tumor progression. Otitis externa can occur if the ears are in the treatment field. This is less severe with daily instillation of ear medication containing corticosteroids, which is started at the onset of treatment. Acute radiation reactions are generally well tolerated and self-limiting. These include epilation, otitis, and when the eyes are included in the treatment field, conjunctivitis, keratoconjunctivitis and corneal ulcers. Acute radiation side effects will subside within 3 - 5 weeks after completion of therapy. Neurologic deterioration may occur as an "early-delayed" or subacute side effect in the 6 to 12 week period after completion of therapy. This subacute toxicity is attributed to capillary permeability changes and transient demyelination secondary to damaged oligodendroglial cells [13]. Patients will usually respond to a course of corticosteroid therapy, improving over several months. However, it is difficult to differentiate subacute toxicity from tumor recurrence.

Late Toxicity of the Brain - Late sequelae to irradiation of brain tissue may appear 6 months to many years after completion of therapy, with the most serious being radiation necrosis [13]. Radiation necrosis can be difficult to differentiate from recurrent tumor. In both entities the patient will have progressive reappearance of clinical signs, an enhancing mass on computed tomographic (CT) images, and surrounding brain edema. Chronic radiation reactions can include permanent skin epilation and pigment change, atrophy of temporal muscle, keratitis with corneal vascularization, cataracts, and deafness. In one study, where brain tissue in the radiation target volume was examined at necropsy in 10 dogs treated with radiotherapy for pituitary macrotumors, demyelination and reactive parenchymal gliosis was observed in dogs where large treatment fields relative to head size were used [22]. Radiation protocol in this study was 4 Gy fractions for 12 treatments [22] and supports the use of smaller fraction sizes when irradiating the CNS. To reduce the probability of late effects to less than 5%, the total dose should be limited to 48 Gy or less in 3 Gy or less fractions [44].

Radiation Toxicity of the Spinal Cord - A transient, reversible myelopathy can occur within 2 - 6 months after completion of radiation treatment of the spinal cord and changes are thought to be related to transient demyelination of the treated length of spinal cord [36]. Chronic progressive or delayed myelopathy can occur months to years after treatment. Permanent myelopathy presents as progressive neurologic signs, including paresthesias, motor weakness, and loss of pain or temperature sensation [36]. The occurrence of this irreversible myelopathy is dependent on total dose, fraction size, and volume of cord treated. In the dog, 44 Gy given in 4 Gy fractions to a 20 cm length of spinal cord has less than a 1% probability for radiation myelopathy [45,46]. In a study evaluating peripheral nerve tolerance of single large radiation doses, the 5% probability of injury (ED₅) for canine peripheral neuropathy was approximately 15 Gy [47]. In that same study, 80 Gy given in 2.67 Gy fractions caused little clinical evidence of nerve injury [47]. This study shows the effect of dose per fraction in irradiation of late responding tissues of the CNS. Radiation injury to peripheral nerve appears to be the result of direct radiation effects on Schwann cells and nerve vasculature and secondary effects resulting from damage to regional muscle and vasculature [48].

Radiation Neuropathy - Radiation neuropathy can occur secondary to the treatment of any tumor when peripheral nerves are in the radiation field. Lameness and muscle atrophy can occur. Documentation of radiation neuropathy in the veterinary

literature has only been reported with single doses of greater than 15 Gy such as given for intraoperative radiotherapy (IORT) [47,49]. There are sporadic case reports of peripheral neuropathy in the human literature [50,51].

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