Radiation Therapy in Veterinary Neuro-Oncology Wednesday, August 3, 2016

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What is radiation therapy?
Radiation therapy (RT) delivers energy (ionizing radiation) to tumors in order to achieve ***local*** disease control. Ionizing radiation either directly or indirectly creates DNA damage; cells with unrepaired DNA double strand breaks subsequently lose reproductive capacity, and often undergo a so-called mitotic death. Less commonly, radiation can directly induce interphase death (apoptosis, as is the case with lymphocytes).

The unit of measurement for radiation dose is the Gray. One Gray equals one Joule per kilogram of irradiated tissue.

Large doses of radiation given all at once overwhelm the repair capabilities of normal tissues, and tumors, alike. As a result, RT has conventionally been delivered in small daily doses (fractions). In this setting, normal tissues of the body can recover from injury more effectively than tumors, which establishes a potential for therapeutic gain. One reason why normal tissues can withstand exposure to ionizing radiation better than tumor cells, is that tumors often have DNA repair deficiencies due to alterations in tumor suppressor genes (e.g., p53, BRCA, etc.).

This situation, wherein radiation damage accumulates in tumor cells at a greater rate than in surrounding normal tissues is particularly advantageous when there is a large burden of microscopic disease surrounding a bulky mass (e.g., pre-operative RT for feline injection site sarcomas), or when a bulky tumor has been surgically removed, and the radiation target is in fact the remaining subclinical disease burden (e.g., post-operative RT for meningioma). In these scenarios, the course of radiation therapy must be effective against tumor cells, but must also be safe for the relatively large volume of normal tissue that is infiltrated by those tumor cells. These are the scenarios where finely fractionated (colloquially referred to as “full-course”, “conventionally fractionated”) radiation therapy is most likely to be of significant benefit.

In physician-based medicine, conventional full-course RT is often delivered 5 days per week for 6-7 weeks. The older literature describes definitive-intent treatments in veterinary medicine that consist of protocols giving 3 fractions per week (Monday-Wednesday-Friday) for about 4 weeks. With improved anesthetic drugs and monitoring, and with the goal of delivering safer and more effective RT, most full-course RT in veterinary neuro-oncology now consists of treatments given 5 days per week for 3.5-4.5 weeks.

How is Stereotactic Radiation Therapy different?
Stereotactic radiation therapy (SRT) represents a departure from this paradigm of protecting normal tissues by delivering high total doses of ionizing radiation therapy in a series of many small daily doses. Instead, SRT delivers very large fractional doses of radiation to tumors, while physically shielding the surrounding normal tissues from exposure to high doses. This is

achieved by employing steep dose gradients, and stereotactic administration of the radiation. Stereotactic administration means that the prescribed dose of radiation can be delivered to a clearly delineated target. Steep dose gradients allow for deposition of high doses of radiation in the tumor, with rapid drop-off of dose outside of the tumor. There are several different types of machines that can be used to deliver SRT. The brand names include Cyberknife, GammaKnife, Trilogy, TrueBeam, and others. Each type of machine uses different techniques and technologies to plan and deliver SRT. But in the end, there are no real differences in the quality of SRT delivered by each of these different radiation units.

SRT delivers large daily doses of RT, but the total dose of radiation is often considerably lower than what is given with conventionally fractionated "full course" RT. Although higher doses of radiation equate to better tumor control when thinking about conventional fractionation schemes, clinical observations make it clear that the lower total doses of SRT can be just as effective (and in some cases, even more so!) than the higher doses of conventional fractionation schemes. There are several possible explanations for this. For example, it is likely that on a Gray for Gray basis, SRT is more biologically effective than full-course RT simply because the treatments are quicker, and there is therefore less opportunity for tumor growth during treatment. There are also some (though not many) tumors (e.g., human prostate carcinoma, and presumably, canine oral melanoma) whose inherent radiosensitivity increases with increasing size of the dose per fraction. Finally, SRT likely has unique impacts on the tumor microenvironment. For example, single fraction SRT has been shown in rodent models to induce rapid vascular endothelial apoptosis.[1] SRT can also transform the immunosuppressive tumor microenvironment by inducing intense CD8+ T-cell infiltrates, and kicking out myeloid-derived tumor suppressor cells.[2]

At the end of the day, what is important to remember is that in physician-based and veterinary neuro-radiation oncology, SRT is delivered 1-5 daily treatment sessions, with the intention of being ablative to all tissues within the high-dose field. Definitive-intent SRT is best reserved for small, well-defined tumors that are not expected to have a large subclinical (microscopic) disease burden. And with few exceptions, it is also important that SRT be reserved for management of bulky (macroscopic) tumors. Because of the ablative nature of SRT, it would be potentially unsafe to apply SRT in the post-operative setting, where the treatment field is occupied by a few cancer cells living in a sea of normal tissue cells!

What are the potential side effects of intracranial RT?

Regardless of whether considering conventional RT or SRT, potential side effects include:

1. Acute radiation toxicity: this is not commonly reported in veterinary medicine, and is most often limited to mild to moderate somnolence during and for a few weeks after completion of RT. This is usually self-limiting, and well-managed by the steroids (most veterinary patients are prescribed an anti-inflammatory dose of orally administered corticosteroids for 4-6 weeks after RT). This may be due to transient peritumoral edema.
2. Early-delayed neuropathy: also referred to as a subacute side effect, and perhaps better described as an encephalopathy (vs. neuropathy), subjects may experience worsening of pre-existing neurologic deficits in the 1-4 months after RT. This is typically mild-to-

moderate, and resolves within a week or two. It is thought to be due to transient demyelination, and may occur in up to 40% of dogs receiving intracranial RT.[3] Treatment is supportive. The biggest challenge is distinguishing this from early tumor progression – therefore, patients with severe or persistent signs should be re-imaged.

3. Late radiation toxicity: brain necrosis is a potentially life-threatening complication of intracranial RT. Fortunately, this is rare, only affecting about 1-2% of patients, and typically taking well over a year to manifest clinically.

Other potential toxicities are linked to proximity of RT fields to normal tissues. For example, patients with olfactory lobe meningioma are at increased risk of developing radiation-induced cataracts, and patients with pituitary tumors may develop late optic neuropathies (due to proximity to the optic chiasm), hypothyroidism and/or diabetes insipidus. Depending on radiation prescription, radiation technique, and tumor location, patients may also experience side effects such as acute dermatitis and/or otitis media. Fortunately, such side effects are uncommon with modern irradiation techniques, such as intensity-modulated RT and SRT.

The reported incidence of these toxicities varies widely in the veterinary literature. This may be influenced by differences in safety of various protocols. However, it is also influenced by differences in post-therapy monitoring, approaches to recording such data, differences in severity of presenting neurologic signs and co-morbidities, etc. For example, it is possible that severely affected patients are overrepresented in papers describing SRT, since families and clinicians may opt for SRT, rather than conventional RT, simply due to the fact that there are far fewer anesthetic events with SRT, even if radiobiologic and clinical considerations suggest that full-course RT may be oncologically superior. These differences, in the absence of prospective comparative clinical trials, make it impossible to accurately predict risk of any toxicity for a given patient, regardless of treatment chosen or disease for which they are afflicted.

Clinical Indication for Radiation Therapy in Veterinary Neuro-Oncology

During the lecture, we will review published and anecdotal experiences relating to management of canine meningioma, canine and feline pituitary tumors, trigeminal nerve sheath tumors, glioma, spinal tumors, and peripheral nerve tumors. We will also briefly discuss the application of craniospinal irradiation, which can be useful for disease such as multifocal metastatic neoplasia, CNS lymphoma, and GME.

References

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3. Griffin LR, Nolan MW, Selmic LE, et al. Stereotactic radiation therapy for treatment of canine intracranial meningiomas. Vet Comp Oncol 2014.