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EDITORIAL

Recent advances in veterinary radiation oncology

Veterinary and Comparative Oncology and *Veterinary Radiology and Ultrasound* have joined forces to create a joint special online issue [Please see link to the Virtual Issue: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1476-5829/homepage/joint_virtual_issue__recent_advances_in_veterinary_radiation_oncology.htm] with a theme of recent advances in veterinary radiation oncology. Associate editors from both journals chose to include studies that exemplify the current state of the art and future directions in our field.

A key factor in implementing new treatments and applying existing protocols to new cases is being able to accurately interpret and reproduce what is reported in the literature. Perhaps in radiotherapy this is a particular concern as much of the veterinary radiation oncology literature to date has been lacking in sufficient detail for this to be done effectively. Keyerleber et al looked at completeness of reporting of patient data, treatment planning, radiation dose, treatment delivery, quality assurance, and adjunctive therapies in published studies in veterinary radiation oncology. Not surprisingly, this study found that in the vast majority of manuscripts, the information provided was lacking or insufficient to allow complete interpretation of results or reproduction of how treatments were planned or done.[1] None of the studies reviewed provided a level of completeness consistent with the guidelines of the International Commission of Radiation Units and Measures (ICRU) and only 24% (11/46) reported more than 50% of the items evaluated.[2,3] The ICRU emphasizes the importance of standardization in reporting for optimal interpretation of clinical results and for repeatability of treatments.[2–5] Adopting standards of reporting for clinical studies as well as reporting of details of radiotherapy planning and delivery are essential to moving forward in veterinary medicine. This paper takes a first step towards this by providing a framework we need to improve how this is done and also a rational set of proposed reporting guidelines that subsequently have been adopted by the editorial board of *Veterinary Radiology and Ultrasound*.[6]

Similarly, defining target volumes during the treatment planning process is a critical step in ensuring optimal clinical outcomes. This is particularly true in the era of conformal radiotherapy, where the expected therapeutic gain as well as the increased risk of missing part of the cancer cell population is impacted heavily by tumour delineation. It follows that accurate reporting of margins around a target is necessary for useful exchange of information between centres and ensures repeatability of results. Christensen et al recently brought awareness of this fact to veterinary medicine and demonstrated that this is an area in which there is still a lot of work to be done.[7] The authors showed that even within a single institution evaluating the contouring of nasal tumours that should be reasonably straightforward to contour, variability in tumour delineation exists. There was enough variation between the clinicians in contouring test data sets that the authors concluded that variability in contouring is a significant barrier to the accurate delivery and reporting of radiation therapy. The authors proposed that guidelines and standardization in contouring are needed to ensure uniformity in treatment. In veterinary medicine, this is particularly important within institutions because most of veterinary radiotherapeutic studies are retrospective and involve a single institution. Christensen et al's paper reminds us to make the effort to establish and follow common contouring practices, regardless of whether we work as solo practitioners or as a team with other radiation oncologists.

A large number of radiation oncology treatments are highly dependent on advanced forms of diagnostic imaging. Traditionally, tumour volumes have been identified using computed tomography (CT) and magnetic resonance imaging (MRI) to provide anatomical localization. Functional imaging may play an increasing role in identifying tumours and defining the tumour microenvironment, which could impact how and where dose is prescribed. Positron emission tomography (PET) is emerging as a potential tool to identify previously undetected extension of disease. A study by Yoshikawa et al begins to explore this area by examining the differences in gross tumour volume in cats with oral squamous cell carcinoma using contrast-enhanced CT or F-fluoro-2-deoxy-D-glucose PET.[8] The authors identified areas on PET imaging that were not visualized by CT. Whilst this work is preliminary and optimal PET imaging agents with greater specificity need to be identified, this study is an early step towards determining the potential of this emerging imaging technique in the optimization of tumour delineation, which is especially important in the context of conformal radiotherapy.

After the acquisition and registration of imaging studies, the next critical step for the radiation oncologist is to accurately delineate both tumour and normal structures. The last 5 years have produced several normal tissue contouring studies that evaluate imaging modalities and consider the challenges presented by inter-fraction motion for both tumour and organs at risk. Multiple studies evaluate the reproducibility of patient positioning using a variety of devices designed for the veterinary patient. This is an essential component of

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determining the planning target volume (PTV). These devices coupled with the use of on-board imaging available on modern linear accelerators such as planar kilovoltage (kV) imaging and cone-beam CT allow for smaller PTVs. Treatments that use high-dose gradients at the margin to decrease dose to surrounding normal tissues need a high level of both precision and accuracy to avoid geographic misses. The study by Hansen et al describes the evaluation and use of one of these devices in determining an appropriate PTV and emphasizes the importance of daily on-board imaging when using advanced radiotherapy techniques.[9]

Fractionation has been a mainstay of definitive radiation therapy for decades. With the advent of intensity modulated radiation therapy (IMRT) and stereotactic techniques, there has been a shift by some groups towards hypofractionation as a potential curative-intent therapy. Clinical experience with new fractionation schemes is needed to assess safety and efficacy compared with standard approaches. In the meantime, biological models to test different fractionation schemes for both tumour control probability (TCP) and normal tissue complication probabilities (NTCP) are useful to determine, at least theoretically, the feasibility of such protocols. Rohrer Bley et al modelled two protocols using different fractionation schemes with the same tumour control probability for brain tumours in dogs.[10] The authors determined that they could safely increase the dose per fraction and decrease the number of fractions without incurring a large risk of late complications for select brain tumours. Through modelling, they identified limitations of tumour size and location on the delivery of hypofractionated treatments, specifically tumours located near the optic chiasm or brainstem. This kind of predictive study may prove informative for the design of thoughtful and efficient clinical trials.

Clinical trials are imperative to bring evidence-based medicine to veterinary radiation oncology. A common challenge that we face in the veterinary profession is the reliance on retrospective studies to assess clinical outcomes. Generally considered a low level of evidence, we rely heavily on retrospective studies in veterinary radiotherapy to make treatment recommendations as well as to plan and carry out treatments. One important limitation of retrospective studies is incomplete or missing data, which can result in bias that makes reproducibility of results improbable. In the time period covered by this review, multiple publications have reported on patient outcomes for many types of tumours using different techniques. It is clear that there has been an increase in the use of highly conformal delivery systems and a move towards hypofractionation. In recent years, we saw the first publications using stereotactic radiosurgery and stereotactic radiotherapy for the treatment of brain tumours. Mariani et al described outcomes for a group of 51 dogs with intracranial tumours treated with a single fraction using a stereotactic technique.[11] The authors showed that the approach can be done safely with a favourable outcome. Griffin et al published a retrospective analysis of stereotactic radiotherapy for the treatment of intracranial meningioma.[12] This study was the first to attempt to define normal tissue tolerance for dogs in the face of hypofractionation. Taken together, stereotactic techniques for brain tumours can be safe and feasible. Their use in the definitive, curative-intent setting requires further validation, however. In line with previous studies, Keyerleber et al recently published a retrospective study of dogs with brain tumours, reporting a longer median survival time associated with conventional fractionation.[13] That study evaluated a standard fractionation, three-dimensional conformal protocol in dogs with and without prior surgical excision of the brain tumour, finding no significant difference in survival between the two groups, and suggesting that radiotherapy alone is a viable treatment with prolonged survival. Whilst conclusions should not be drawn from comparison of uncontrolled studies, these data in dogs with brain tumours treated with stereotactic hypofractionated protocols or conventional protocols remind us that prospective clinical trials are needed to answer lingering questions about efficacy outcomes such as survival.

Hypofractionated stereotactic protocols have also been investigated in areas outside of the cranium. Gieger et al recently published a case series of nasosinal tumours treated with a linear accelerator-based hypofractionated stereotactic protocol in 29 dogs.[14] Encouragingly, median survival was similar to that reported for fractionated protocols, supporting the potential role of hypofractionated stereotactic radiotherapy in curative-intent treatment of dogs with intranasal tumours. As hypofractionated treatments increase the potential for normal tissue complications, case selection may be important in determining which cases are suited for high dose per fraction stereotactic protocols, as Rohrer Bley's modelling study suggested. The idea of case selection bore true in Kubicek et al's retrospective analysis of dogs with osteosarcoma treated with stereotactic radiosurgery.[15] That study showed that risk of fracture after a single ablative dose of radiation was more likely to occur in dogs presenting with subchondral bone involvement. This highlights the importance of identifying patients that may be best suited for these types of procedures.

As evidenced by the collection of publications in this editorial, our profession's forward momentum appears to be towards the use of sophisticated approaches for more convenient and conformal curative-intent treatments. Despite these advancements that improve our ability to deliver precise, conformal treatment, few would contest the important role radiotherapy plays in palliation in veterinary medicine. Our potential impact to ameliorate the lives of dogs and cats with cancer is probably broader when it comes to simple palliative approaches than more costly sophisticated treatments. Multiple studies have been published in both journals in the past 5 years evaluating radiation in the palliation of cancer. Tan-Coleman et al published a 4 Gy × 5 daily fraction protocol for the palliation of nasal tumours in dogs, which had positive results in terms of relief of clinical signs and in prolonging life.[16] The novelty of this protocol lies in its lower dose per fraction compared with previously published palliative schedules, its short overall duration and, importantly, the potential for re-treatment in the palliative setting. For these reasons, we believe that this protocol will be widely used as a palliative treatment option for multiple tumour types in upcoming years.

Veterinary radiation oncology continues to make progress in the implementation of new technologies, techniques, and protocols whilst increasing knowledge of patient outcomes. We still face knowledge gaps, and need controlled clinical trials to determine true patient outcomes, prognostic factors, dose tolerances, and toxicities. Given the increased costs associated with these newer technologies and the increased requirements in personnel and quality assurance that they require, we would be remiss not to do a rigorous and thoughtful cost-benefit analysis of our impact on our patients and our pet-owner clients as we move into the next phase with these rapidly paced and broadly implemented advances in veterinary radiation oncology.

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