Principles and Practice of Radiation Therapy in Exotic and Avian Species

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Abstract
Radiation therapy has long played a significant role in the treatment of cancer in people, dogs, and cats. Recently, this technology has been applied to small mammal, avian, and reptile species with some success. Radiation therapy may play an important role in the control of locally aggressive tumors and has been used in both definitive and palliative settings. However, there are some special challenges that must be overcome to successfully treat these species with radiation therapy and, in many cases, little is known about the natural behavior of the tumors being treated. This article introduces some of the basic tenets of radiation oncology, while addressing some of the aspects of radiation biology that are problematic when treating very small or air-filled patients. Much work needs to be done to define fractionation schemes and field geometries that will allow avian and exotic pets to be safely and effectively irradiated. Copyright 2005 Elsevier Inc. All rights reserved.

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Radiation therapy is a powerful adjunct to surgery when complete resection of a tumor is not possible. The combination of surgery plus radiation therapy will frequently result in better local control of a tumor than would have been achieved with either modality alone, without significantly increasing patient morbidity. Radiation therapy may also be used in a palliative setting to relieve discomfort or obstruction with or without adjunct surgery.

Exotic animals and birds have been successfully treated with radiation therapy,[1-8] although there are some special challenges that must be met to safely and effectively treat these species. Historically, much of the literature dealing with radiation therapy for small mammals and birds has been generated in a research setting. Our current challenge is to gain an understanding of the clinical applications of radiation therapy in these species with spontaneously developing tumors.

Principles of Radiation Therapy

Radiation therapy results in cellular damage by the process of ionization, which is the ejection of an electron from a cellular component of the absorbing material. This ionization reaction results in the for-

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mation of highly reactive radical species, which account for the biologic effect of radiation therapy.[9,10] The ionization may occur intranuclearly, within the DNA itself, in which case it is termed a direct action of ionizing radiation. More commonly, however, the ionization occurs in some other intracellular component, primarily water or oxygen, and is termed an indirect action. The free radicals produced by the indirect actions of radiation therapy play a critical role in the cellular response to radiation, because the superoxide and hydroxyl radicals most commonly produced result in significant cytotoxic stresses to the cell.[9] It is generally recommended that free radical scavengers and antioxidants be avoided during radiation therapy if possible.

Tumors arising from different tissues have differing levels of inherent radiosensitivity.[11] As a rule of thumb, tumors arising from hematopoietic tissues are the most radiosensitive, followed by those of epithelial origin, with mesenchymal tumors being the most radioresistant. This does not mean that a mesenchymal tumor cannot successfully be treated with radiation therapy. However, a higher cumulative dose of fractionated radiotherapy will be required to achieve local control for a fibrosarcoma than would be necessary, for example, to control a solitary hematopoietic tumor like an oral plasmacytoma.

There are multiple factors that influence the inherent radiosensitivity of a tumor, such as doubling time, growth fraction, and hypoxia.[11] As with cytotoxic chemotherapy, those cells rapidly moving through the cell cycle are most susceptible to the effects of radiation therapy, with cells in the M phase of the cell cycle being the most sensitive.[12] It is beyond the scope of this article to discuss the radiobiologic reasons for this cell cycle effect, but the clinically significant application of this principle is that radiation therapy will rarely be successful when used as primary therapy for a large, slowly growing tumor with a large number of cells in the resting phase (G_0) of the cell cycle (Fig 1). Additionally, large tumors will frequently develop areas that expand beyond the capillary diffusion radius of oxygen, resulting in hypoxic regions. These zones of hypoxia will significantly reduce the local control probability for an individual tumor. This phenomenon, experimentally known as the oxygen enhancement ratio, stems from the fact that hypoxic cancer cells are inherently more radioresistant than their well-oxygenated counterparts.[10,11] These physical characteristics of large tumors collectively result in primary radioresistance, forming the basis for the recommendation of surgical cytoreduction before the initiation of radiation therapy. Although there are some theoretical advantages to performing radiation therapy before surgery,[13] this approach has not proven to be clinically superior to postoperative radiotherapy in other species and has a higher surgical complication rate.[14,15]

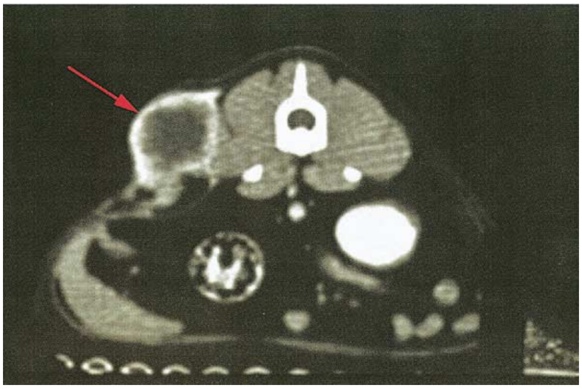

Figure 1. Contrast-enhanced CT scan in a feline patient with a large, ring-enhanced sarcoma involving the right dorsolateral flank region. A contrast-enhancing ring (arrow) may be seen around the well-vascularized periphery of the tumor, with the poorly enhancing central region representing a zone of hypoperfusion and hypoxia.

Radiation therapy is delivered in multiple treatments called fractions. The dose of radiation delivered per fraction will have a significant effect on both the local control achieved and the severity and type of toxicity encountered. Generally speaking, definitive protocols consist of 12 to 21 fractions of 2.5 to 4 Gy delivered over 4 to 7 weeks.[16] These protocols deliver a high total cumulative dose and are the most likely to result in long-term local control. Palliative protocols tend to be delivered as single weekly fractions of 8 to 10 Gy for 3 or 4 consecutive weeks[17] and may be used in emergency situations to rapidly relieve pain or physical obstruction (Fig 2). These high-dose-per-fraction protocols are less likely to result in long-term tumor control. However, some patients treated with high-dose/high-fraction protocols will have a significant and durable response to treatment.[18-22] These high-dose-per-fraction protocols may be appropriate choices for exotic animal species, because they minimize the handling and anesthesia requirements necessary to deliver a therapeutic dose of radiation.

Radiation toxicity is encountered in both acute and delayed forms. Acute radiation toxicity is most commonly seen in the low-dose-per-fraction definitive protocols, where a high total cumulative dose is delivered in many fractions with curative intent. Acute radiation toxicity will usually be encountered toward the end of the treatment cycle and is manifested most frequently as radiodermatitis and mu-