Radiation-induced Osteosarcoma in Dogs after External Beam or Intraoperative Radiation Therapy

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ABSTRACT

This report describes radiation-induced osteosarcomas in two groups of dogs. One group was given radiation therapy for spontaneous tumors and the second group of normal adult beagle dogs was given experimental intraoperative radiation therapy. Secondary tumors developed between 1.7 to 5 years after irradiation. Three of 87 spontaneous tumor-bearing dogs or 3.4% of dogs treated for soft tissue sarcomas developed osteosarcoma within the field of irradiation. Twenty-two dogs or 25% of dogs treated for soft tissue sarcomas survived 20 months. This high incidence may be due to the use of fractions in excess of 3.5 Gy. These dogs received 10 fractions in 3 weeks with fractions ranging from 3.5 to 5.0 Gy. Tumor induction may be included in the late effects of irradiation which are worsened by the use of coarse fractionation. There appeared to be a dose relationship for tumors induced after single intraoperative radiation doses combined with fractionated external beam irradiation. Seven of 27 dogs given this treatment and surviving at least 4 years developed osteosarcomas in the field of irradiation. One of 26 dogs given intraoperative radiation alone developed a tumor between 4 and 5 years. The lower incidence after intraoperative radiation alone may have been due to the lower total dose. However, the sequence of a course of fractionated irradiation followed by a large single dose seemed to enhance carcinogenicity.

INTRODUCTION

Radiation-induced osteosarcoma is a rare but well recognized phenomenon in human radiotherapy patients (1-8). It was first reported in the 1920s by Beck in patients after treatment with ionizing radiation (9). One report on two cases of osteosarcoma after radiotherapy for spontaneous tumors in dogs was found (10). Two reports of radiation-induced osteosarcomas in experimental dogs after external beam or intraoperative irradiation are known (11, 12). In 1929 the appearance of osteosarcoma after ingestion of 226Ra was observed in radium dial painters (13). Induction of bone tumors in dogs after ingestion of bone-seeking radionuclides also has been demonstrated (14). There are no significant structural differences between bone tumors in humans and dogs. Induction of osteosarcoma is thought to be associated with morphological changes in bone (15-16). Risk estimates for radiation-induced osteosarcomas are difficult to make because of the small number of cases involved. Incidence varies with the site irradiated; the scapula and humerus are common sites in humans (5, 8). Experimental studies have shown that incidence also varies with total dose, dose rate, and dose fractionation and perhaps sequence (17, 18). The incidence of development of osteosarcoma was recently estimated at 1% for patients surviving 8 years after radiation therapy for Hodgkin's disease and at 0.05% after irradiation for breast cancer (1, 2, 19). One institution reported that 5.5% of all osteosarcomas registered occurred after exposure to X-rays (3). These tumors are aggressive and survival of radiation-induced osteosarcoma patients is poor (6).

MATERIALS AND METHODS

The cases discussed in this report come from either randomized clinical trials on tumor-bearing dogs (Group 1) or an experimental study in normal beagle dogs (Group 2). In the clinical trial, 87 dogs with various soft tissue sarcomas were admitted to Colorado State University Veterinary Teaching Hospital. Pretreatment biopsies were done on all dogs. Dogs which had hemangiopericytomas, fibrosarcomas, or neurofibrosarcomas and given radiation therapy were included in this study. None of the dogs had previous chemotherapy or radiation therapy, although some tumors were recurrent after surgery. Dogs in Group 1 were randomized into two studies. The first study was on the use of the radioprotector WR-2721. Dogs were randomized to receive total doses between 35 and 50 Gy, with or without radioprotector. Results from this study have been published (20, 21). The second study involved the use of local ultrasound hyperthermia plus irradiation for the control of soft tissue sarcomas. Dogs were randomized to receive between 35 and 50 Gy, with or without hyperthermia in this ongoing study. A 6-MV1 clinical linear accelerator was used for all irradiations. Doses were delivered in 10 fractions on a Monday, Wednesday, Friday schedule over 22 days. The size of dose per fraction varied from 3.5 to 5.0 Gy to achieve the desired total dose.

In Group 1, studies 1 and 2, 1, 3, 6, and 12 months after treatment and every 6 months thereafter. The tumor site was evaluated for tumor growth and normal tissue response. Dogs were returned to Colorado State University for necropsy at the time of euthanasia or death. Biopsies were obtained from the second primary tumors. Comparisons were made between biopsies from the first and second primaries. The biopsies of the primary tumors were reviewed by two independent pathologists.

In Group 2, 67 normal 1-year-old beagle dogs were randomized into one of three treatment groups and survived at least 4 years. Dogs received either fractionated doses of EBRT between 60 and 80 Gy, IORT single electron doses between 25 and 47.5 Gy, or a combination of 50-Gy fractionated external beam plus single intraoperative doses for total doses between 75 and 97.5 Gy (Table 1). Dogs receiving EBRT only were given 30 fractions of 2.3 or 2.67 Gy/fraction. Dogs receiving the combination were given twenty-five 2-Gy fractions in 5 weeks plus IORT at week 6 so that the total irradiation times were equal.

All external beam irradiation was done by using photons from a 6-MV linear accelerator. Intraoperative irradiation was done by using 6 MeV electrons from the same machine. The fields included the aorta, peripheral lumbar nerve, left ureter, and the ventral lumbar vertebrae L4 through L6. Dogs were observed for 5 years after treatment. Dogs were housed in outdoor runs with shelters and were given dog chow and water ad libitum. Serum chemistries, complete blood counts, urine analysis, plain film radiographs, i.e. pyelograms, and aortograms were done prior to and at designated intervals after treatment. Eight dogs were euthanized during the fourth year, three of these were related to the presence of tumors. All other dogs were euthanized as scheduled at 5 years. Further details and results have been published (22-25).

1 The abbreviations used are: MV, megavoltage; EBRT, external beam radiation therapy; IORT, intraoperative radiation therapy.

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RESULTS

Group 1. Spontaneous Tumor-bearing Dogs

Radiation-induced osteosarcomas developed in 3 of 87 dogs treated with radiation therapy for soft tissue sarcomas. Only 22, or 25% of these 87 dogs survived 20 months or longer.

Case 1. A 7-year-old intact male malamute was admitted for treatment of a recurrent fibrosarcoma of the right midthorax which was 120 cm². The mass was given 35 Gy of 6 MeV electrons in 10 fractions to an area 14 x 14 cm. Four months postirradiation the tumor had increased in size and was surgically excised. At 2 years there was no evidence of the primary tumor. At 3 years and 2 months a s.c. mass was noted in the field of irradiation. The mass was identified as osteoblastic osteosarcoma by histology.

Case 2. An 8-year-old St. Bernard cross was admitted for treatment of a 40-cm² hemangiopericytoma on the caudal lateral aspect of the left thigh. The tumor was given 35 Gy of 6 MV photons in 10 fractions to an area 10 x 14 cm. Twenty months after treatment of lytic bone lesion of the middiaphyseal femur occurred within the field of irradiation.

Case 3. A 10-year-old female mixed breed German shepherd received radiation therapy for a 24-cm² fibrosarcoma involving the gingiva of the right canine tooth. The tumor was given 42.5 Gy of 6 MV photons in 10 fractions plus 7 treatments of ultrasound hyperthermia. The field size was 8 x 8 cm. At 2 years and 5 months the animal appeared to be free of disease. One month later the dog developed swelling of the right maxilla. The mass was diagnosed as osteoblastic osteosarcoma.

Group 2. Experimental Intraoperative Radiation Therapy Study

Eight radiation-induced osteosarcomas occurred after experimental intraoperative radiation therapy (Table 1). There were no radiographically detectable lesions in these dogs prior to irradiation. In this study, 14 dogs were given fractionated external beam therapy alone to the same field. No osteosarcomas were seen within 5 years after irradiation in dogs given EBRT alone. Of 26 dogs given IORT, only 1 dog given 47.5 Gy developed an osteosarcoma (Table 2). A high incidence of osteosarcoma occurred in the dogs given a combination of IORT plus EBRT. Of 27 dogs, a total of 7 cases occurred. No evidence of metastatic disease was found in any of these dogs.

The tumors developed within the lumbar vertebrae in 6 dogs and within the psoas muscle in 2 dogs. Tumors in the psoas muscle were poorly differentiated and formed scint tumor osteoid. Four of the six tumors in the vertebrae were osteoblastic with abundant tumor osteoid, bone and variable cartilage formation. The other two vertebral tumors were poorly differentiated.

DISCUSSION

Total dose and dose per fraction have been shown to influence neoplastic transformation in vitro and in vivo (26-28). A recent review of second cancers after brachytherapy for tumors of the cervix showed a dose-response relationship (29). In that study an overall relative risk of 1.3 was observed for induction of bone cancer. Relative risk reached 3-fold for bone doses greater than 10 Gy. Little information is available on risk estimates in the high dose ranges often received by bone in patients receiving external beam radiotherapy.

The incidence of radiation-induced osteosarcoma in this study for dogs surviving at least 20 months after therapy for soft tissue sarcomas (Group 1) was unusually high. Three of 87 dogs treated developed osteosarcoma in the field of irradiation. However, only 22 of 87 dogs survived long enough to be a risk for radiation-induced tumors. The total doses used in this study were relatively low, ranging from 35 to 42.5 Gy. No evidence suggesting an increased susceptibility of dogs to radiation-induced tumors is known to date. The high incidence may be due to the use of large doses per fraction (26).

Coarse fractionation has commonly been used in veterinary medicine due to the requirement for anesthesia for immobilization during treatment. Recent advances in veterinary anesthesia allowing more frequent anesthesia and recognition of the increased late effects produced by coarse fractionation are beginning to change this. It should be noted that the incidence of spontaneous osteosarcoma in dogs is higher than that of humans (13). Large breed dogs are said to be 61 times more likely to have osteosarcoma than small breeds (13). However, the tumors in this study did not occur at the sites most common for spontaneous osteosarcoma. Spontaneous osteosarcomas most frequently occur at the metaphysis of long bones in both humans and dogs (13). The dogs in this study developed osteosarcoma in the skull, chest wall, vertebrae, and middiaphyseal femur. Radiation-induced tumors may occur at variable sites. Two of the tumors in the study of dogs with soft tissue sarcomas and all 8 tumors in the experimental study occurred in fields in which large surface areas of trabecular bone were irradiated such as on the chest wall, skull, or vertebrae. A strong correlation has been shown between the reported tumor frequency in radium- and non-radiation-induced osteosarcoma in humans and large trabecular bone areas (30). This may also contribute to the incidence of radiation-induced tumor in Hodgkin's disease patients in which large volumes of bone are irradiated. The improved survival of patients with Hodgkin's disease certainly contributes to the recognition of this late effect of irradiation (4).

All cases in Group 2 meet the criteria for radiation-induced tumors established by Cahan (31). Specifically, (a) there was no radiographically detectable lesion in the affected bone prior to irradiation; (b) the osteosarcoma developed in the area included in the radiation field; (c) the tumor was confirmed histologically; and (d) there was a long asymptomatic latent...
period of 4 to 5 years. Two of the 3 cases in Group 1 also meet these criteria. The third case does not as it had bone lysis with the original mass; however, the lesion was most consistent with secondary bony invasion rather than osteosarcoma, and two independent pathologists diagnosed this tumor as fibrosarcoma. The biological behavior was also unlike for an osteosarcoma. Furthermore, radiographically the bony lesions had resolved after tumor regression following radiotherapy.

The latency time for tumor induction in Group 1 dogs ranged from 1.7 to 3.2 years. Latency times in humans range from 14 months to 33 years (6). Median latency times of 10 or 11 years have been calculated from two series with large numbers of patients (2, 6). The latency time in dogs would be expected to be shorter due to the shortened life span. It is estimated that a year of a dog’s life is roughly equivalent to 7 years of human life.

The latency time was 4 to 5 years in Group 2. This is longer than the latency period seen for spontaneous tumor-bearing dogs (Group 1) in this report. This may be due to an increased resistance of healthy young adult dogs. Beagles were between 1 and 2 years old at irradiation. As these dogs were euthanatized between 4 and 5 years it is not known whether or not more tumors would have developed with time. It is also interesting to note that no metastatic disease occurred in the normal dogs. This also may be influenced by the dogs being euthanatized at 5 years. The average age of the tumor-bearing dogs (Group 1) at irradiation was 7 years. The disturbance of the normal tissues by the primary tumor may also be a factor in shortened latency times. Another point of consideration in these cancer patients is that of an inherent predisposition for the development of a tumor (32). The unlikely possibility of these tumors being second primaries also exists (10).

The incidence of osteosarcoma after experimental intraoperative radiation therapy is disturbingly high in this study (Table 2). The overall incidence was 8 of 53 dogs or 15% of all dogs given intraoperative irradiation and surviving at least 4 years.

The incidence of spontaneous osteosarcoma in beagle dogs is very low (13). Of 14 beagles given external beam irradiation at 60, 70, or 80 Gy in 30 fractions, no osteosarcomas were seen within 5 years. When IORT was given alone one osteosarcoma was seen 4 years after 47.5 Gy. The combination of 50 Gy EBRT followed by IORT was very efficient at tumor production. Tumor induction appeared to increase with increasing dose between 47.5 and 90 Gy (Table 2). Incidence decreased at 97.5 Gy total dose which may be due to chance; however, increased cell killing at this dose may have reduced the chance of a carcinogenic event occurring (33). Two of the dogs given 47.5 Gy IORT plus 50 Gy EBRT that did not develop tumors had septic osteoradionecrosis with very few viable bone cells present (22). One hypothesis states that induction of tumors by radiation has both a direct and indirect effect (18). The direct effect was described as a malignant change in the regenerating cells and the indirect effect as creating an environment for expression of that malignant change. This would involve changes in connective tissues and vessels. Stromal damage has been shown to be more severe with large single doses and may contribute to the incidence of tumor induction after intraoperative irradiation.

Studies of skin tumor induction in rats has shown that carcinomas arose only when previous signs of radiation erythema and inflammation were present and then additional irradiation was done (18). This may be similar to the situation in our dogs given combined EBRT plus IORT. Early vessel damage and inflammatory change induced by the EBRT likely were present at the time of delivery of the IORT dose.

In other experimental animals osteosarcomas were associated with vascular damage, osteoblast depletion, and later reactive hyperplasia and osteoscleroderma (15). A recent report on radiation-induced osteosarcoma in mouse vertebrae stated that repetitive irradiation was more effective at tumor induction (28).

In humans, the microscopic appearance of radiation-induced sarcomas is similar to that in spontaneously observed cases, and slightly over 50% are poorly differentiated (6, 15). Osteosarcoma is the most common histological type of radiation-induced sarcoma (6, 15). In the dogs in this study, all tumors were osteosarcomas and these resembled spontaneously occurring nonradiation-induced osteosarcomas in dogs. Five of eight tumors were poorly differentiated and the remainder were osteoblastic or chondroblastic. Interestingly, in the dogs given experimental intraoperative radiation the more poorly differentiated tumors occurred at the lower radiation doses. Three dogs given intraoperative irradiation and one cancer patient had osteosarcoma arising primarily in soft tissue. Extraskeletal osteosarcoma has also been reported in humans and 5.7% of these were secondary to irradiation (34). Regardless of site or histological type, radiation-induced osteosarcomas in humans have a poor prognosis (15) as did the dogs in this study.

An estimated 20-fold increase of second cancers occurs following treatment of childhood malignancies (35). Intraoperative irradiation has been used on pediatric patients (36). Long-term observation of these patients is being done. Evaluation of tumor induction by IORT in adult patients is also needed. The lowest IORT dose associated with tumor induction in this study was 25 Gy. Currently, IORT doses of 15–20 Gy are most commonly used (23). The risk of tumor induction may be less at these lower doses. The risk of tumor induction should be included in the evaluation of new therapeutic modalities.

REFERENCES


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