Evaluation of Intraoperative Radiation Therapy for Incompletely Resected or Recurrent Canine Hemangiopericytomas: Seventeen Cases

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ABSTRACT

The objective of this study was to evaluate conservative surgery and intraoperative radiation therapy (IORT) for incompletely resected or recurrent hemangiopericytoma. Dogs that had been resected at our faculty and diagnosed as incompletely resected or recurrent hemangiopericytoma were studied. Dogs that had previously undergone surgery or had frequent radiotherapy were excluded. Seventeen dogs met these criteria, of which 10 underwent surgery alone (surgery group), and 7 underwent consecutive surgery and IORT (IORT group). After resection of the tumor, an acrylic cone was set to irradiate underlying tissue and avoid surrounding skin. The tumor bed was irradiated with a 3-MeV electron beam. The median radiation dose was 10 Gy (range, 10 – 15 Gy). After IORT, the incision was closed in a routine manner. Ten tumors recurred locally, 6 of 10 (60%) of the surgery group and 4 of 7 (57%) of the IORT group. Tumor-free survivals were 441 days (range, 183 – 1,071 days) in the surgery group and 810 days (range, 660 – 1,576 days) in the IORT group. The IORT group had significantly longer tumor-free survival than the surgery group ($p = 0.043$). No radiation side effects were detected. Although the recurrence rate was not significantly different with or without IORT, consecutive surgery and IORT may be able to prolong tumor-free survival without radiation side effects.

Figure 1 *IORT After resection of the tumor, stay suture was placed on surrounding skin and suitable cone are inserted. The tumor bed was irradiated by a 3-MeV electron beam, median 10 Gy (10-15 Gy).*

INTRODUCTION

Hemangiopericytoma (HPC) is very common in middle-aged or older dogs.[1] Soft tissue sarcomas are a heterogeneous population of mesenchymal tumors that include hemangiopericytoma.[2, 3] Soft tissue sarcoma has a similar pathologic appearance and clinical behavior. These tumors originate in connective tissues, including muscle, adipose, neurovascular, fascial, and fibrous tissue.[2] In contrast to many other malignant tumors, soft tissue sarcomas rarely metastasize.[3] If metastasis occurs, it is usually late in the course of disease. Therefore, local treatments such as surgery and radiation therapy are potentially curative if used appropriately and early.[4] In cutaneous soft tissue sarcoma, surgical margins should include the fascial plane below the clinically detectable tumor or 2 to 3 cm of tissue in all surgical planes around the palpable tumor.[3, 4] Surgical margin is prognostic for local recurrence.[3, 5, 6]

The recurrence rate of canine soft tissue sarcoma without radiotherapy has been reported as 7.4%5 and 15%,[6] and the recurrence rate of canine hemangiopericytoma without radiotherapy has been reported as 26%7 and 38%.8 When tumors involve the limb, amputation greatly increases the likelihood of long-term control.[4] Postorino reported that the mean time to recurrence with or without radiation therapy after surgery was 27 and 16 months, respectively.[7] They concluded that radiation therapy is useful as an adjuvant when complete excision is impossible. Moreover, radiation therapy alone is used to treat cases of unresected tumor or unwillingness to amputate the limb with tumor. In canine soft tissue sarcoma, a 1-year control rate of 67% was obtained by radiotherapy alone at a dose of 50 Gy.[9] Around 10 fractions of extra-beam radiation therapy with or without surgery were needed,[7, 9] which is a heavy burden for the pet dog and owner.

At the time of surgery, irradiation of the tumor bed may prolong tumor-free survival. Intraoperative radiotherapy (IORT) has been performed for some tumors such as prostatic carcinoma,[10] prostatic tumor,[11] and extracorporeal irradiation for limb sparing[12, 13] in dogs. The purpose of this study was to describe the effects of resection and IORT for canine HPC.

MATERIALS AND METHODS

A total of 202 dogs were referred to the Oncology Department of Azabu University Veterinary Teaching Hospital between 1985 and 2007. In this study, dogs that had been resected at our faculty and diagnosed as incompletely resected or recurrent hemangiopericytoma were evaluated. The exclusion criteria were previous surgery or frequent radiotherapy.

Information obtained from the medical records included breed, sex, age, tumor location, with or without IORT, surgical margin, mitotic index, recurrence, tumor-free survival, irradiation dose, and radiation side effects. Follow-up data were obtained for every case, and the median follow-up time was 735 days (range, 374 – 1997 days).

For radiation therapy, a 4-MV linear accelerator (Mevatron, Toshiba, Tokyo, Japan) was used. After resection of the tumor, an acrylic cone was set to irradiate underlying tissue and avoid surrounding skin. Stay sutures were placed in the skin to maintain the situation during radiotherapy. The stay sutures were temporarily lifted and fixed to the cone by sterilized self-adherent bandaging tape (Vet Wrap, 3M, St. Paul, MN), and the tumor bed was irradiated by a 3-MeV electron beam (Fig. 1). Immediately after IORT, the stay sutures were removed, the operation field was flushed, and the incision was closed in the routine manner.

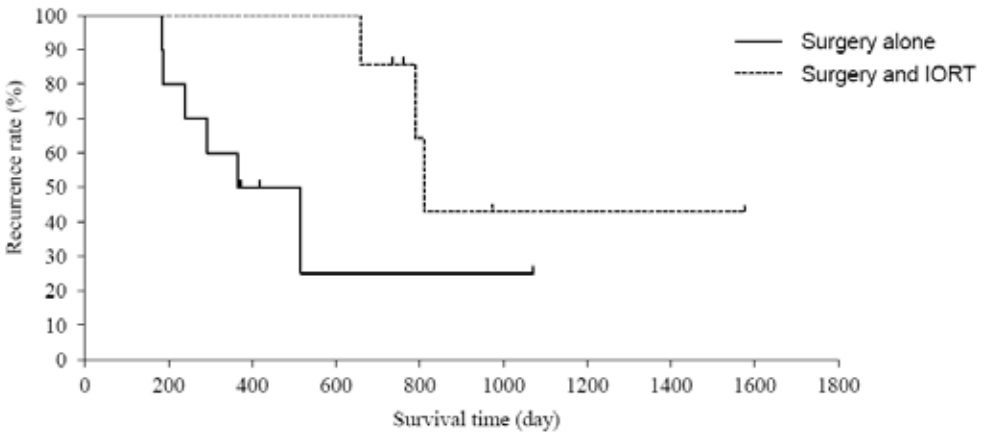
The treatment group was divided into the surgery alone (surgery alone group) and the surgery and intraoperative radiation therapy (IORT group) groups. The recurrence rate and tumor-free survival were compared between the two groups. Fisher's exact test was used to identify IORT efficacy based on the recurrence rate. The Mann-Whitney U test was used to assess the mitotic index, which was classified into three groups (<10, <20, and ≥20). To estimate tumor-free survival, Kaplan-Meier survival analysis was performed. The difference in tumor-free survival with or without IORT was analyzed using the log-rank test. The level of significance was set at $p < 0.05$.

RESULTS

A total of 17 dogs (7 males, 10 females; median age 11.0 years; and age range 5.8 – 14.4 years) met the inclusion criteria, including 15 margin-dirty cases and 2 margin-clean but recurrent cases. The common breeds were Shiba Inu (n = 4), Siberian Husky (n = 3), and Shetland Sheepdog (n = 3). The other breeds were Shih Tzu, Golden Retriever, Beagle (n = 1 each), and mixed breed dogs (n = 4). The dogs' median body weight was 12.6 kg (range, 4.8 – 40.0 kg). The tumor was located in the forelimb (n = 11), hindlimb (n = 4), and trunk (n = 2). Amputation was not performed for all limb tumors.

Of the 17 cases, 10 were in the surgery group and 7 were in the IORT group. Ten tumors (59%) recurred locally. On histopathology, the surgical margin was dirty in nine

Figure 2*Tumor-free survival time Kaplan-Meier survival method was applied to estimate tumor-free survival. Tumor-free survival of surgery alone group, and IORT group were 441 days (range, 183 – 1071 days) and 810 days (range, 660 - 1576 days), respectively.*



and clean in one in the surgery group, with the clean margin case showing recurrence, while in the IORT group, the surgical margin was dirty in six and clean in one, with the clean margin case showing recurrence. The mitotic index could be evaluated in 13 cases. The mitotic index was <10 in one of each group, <20 in two of each group, and ≥20 in four of the surgery group and three of the IORT group. More than half of the cases were ≥20, and there was no significant difference between the groups. Recurrence was seen in 6 of 10 (60%) cases in the surgery group and 4 of 7 (57%) in the IORT group. No significant difference was found between the groups. Tumor-free survival was 441 days (range, 183 – 1071 days) in the surgery group and 810 days (range, 660 – 1576 days) in the IORT group (Fig. 2). Tumor-free survival was significantly longer in the IORT group than in the surgery group ($p = 0.043$). For IORT, the median cone size was 4 cm (range, 3 – 8 cm), and the median radiation dose was 10 Gy (range, 10 – 15 Gy). No radiation side effects were detected.

DISCUSSIONS

The results of this study show that conservative surgery and IORT can prolong tumor-free survival without radiation side effects, but cannot reduce the local recurrence rate. Tumor-free survival was significantly longer with IORT (810 days) than with surgery alone (441 days; $p = 0.043$), and there was no evidence of side effects from IORT, but the local recurrence rate was not significantly different between surgery alone and surgery with IORT.

Kuntz et al. reported that complete removal of tumor margins was prognostic for local recurrence, and complete margins and mitotic rate were significantly prognostic for survival time.[6] Stefanello et al reported that marginal surgical excision without adjuvant treatment of low-grade soft tissue spindle cell sarcoma of the extremities resulted in a low local recurrence rate (10.8%).[14] The recurrence rates of other reports, such as Kuntz et al (28%)[6] and Forrest et al (15%),[15] were higher than that of Stefanello et a. (10.8%).[14] The mitotic rate may be an important prognostic factor. In the present cases, the mitotic rate was ≥20 in more than half, and it was thought that this high mitotic rate caused the high local recurrence rate (59%).

Radiation side effects were not noted clinically because surrounding skin was avoided. Hoekstra et al reported that a dose of 20 Gy was generally well tolerated without significant increased treatment morbidity for dogs,[16] but higher doses (over 30 Gy) have produced radiation-induced sarcomas in some animals followed over a long period. Others reported that the frequency of radiation-induced malignancies in dogs given ≥25 Gy was 21% to 25%.[17, 18] For this report, the tissues underlying the radiation field were muscle and bone. Radiation side effects affecting muscle and bone are muscle fiber loss and bone necrosis or fracture, respectively.[19] Powers et al reported that IORT doses of 10 to 15 Gy have an effect at least five times greater than the 50 Gy in 2 Gy fractions for late-responding normal tissues.[18] Thus, in the present study, the median electron beam dose was 10 Gy. Furthermore, the depth dose of the electron beam increases with increasing energy of the electron beam. The 3-MeV electron beam in the present study reaches a depth of only about 1 cm, and it was sufficient to irradiate the surface of the limb or thoracic wall.

IORT can be combined with postoperative radiotherapy. With this combination, radiation side effects affecting the skin are thought to be minimized due to irradiation within the tolerance dose of normal tissue. This combination should also prolong tumor-free survival, because the irradiation dose to the tumor bed is higher than with each treatment alone. However, the dose to the tumor bed exceeds the tolerance dose of normal tissue. Radiation side effects of muscle are a minor problem because of fibrosis, but radiation side effects of bones are major problems, including necrosis and fracture. For this reason, the combination of IORT and postoperative radiotherapy may

be harmful, depending on the underlying tissue.

When hemangiopericytoma occurs in elderly dogs, if local control is achieved for a few years, the dog may be able to live for many years without amputation. In this case, conservative resection and IORT may be able to control local tumor without an adequate margin, such as with limb sparing or marginal resection of the trunk.

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