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Combination Therapy of Hypofractionated Radiotherapy and Surgical Resection for Canine Intranasal Tumors

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Abstract:Untreated canine intranasal tumors have a poor prognosis. The median survival time of dogs with intranasal tumors when treated with hypofractionated radiotherapy alone does not typically exceed one year. In this retrospective study, we evaluated dogs treated with hypofractionated radiotherapy followed by surgical debulking. Among 18 dogs, four had stage I, one had stage II, five had stage III, and eight had stage IV tumors. Surgery was performed either immediately after the final radiation treatment or 1–2 months after radiotherapy. Following macroscopic tumor resection after surgery ($p = 0.008$), the timing of surgery ≥ one month post-radiotherapy ($p = 0.011$) and the early tumor stage (I–III; $p = 0.043$) were potentially associated with a favorable progression-free survival. The median overall survival in the early stages was 26 months. Therefore, microscopic residual tumor resection should be considered one month after completion of hypofractionated radiotherapy for dogs with early-stage tumors.

Keywords: canine, hypofractionated radiotherapy, intranasal tumor, surgery

Introduction

Generally, dogs with intranasal tumors have a poor prognosis, and a significantly increased survival time could be expected with radiotherapy[1)]. Surgical resection alone does not significantly improve survival time as complete removal of the tumor is practically impossible because of its anatomic location and the large extent of the disease at the time of diagnosis[2,3)]. Therefore, radiotherapy without chemotherapy or surgery is considered the standard treatment of choice[1,4)], with reported median survival ranging from 5 to 19.7 months[5-17)].

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In general, fine fractionated protocols associated with a higher total dose are considered superior to hypofractionated protocols for tumor control. However, local tumor recurrence is still common, even with the use of fine fractionated radiation protocols and megavoltage teletherapy equipment[4,6,7,13,15,18-21)]. Therefore, various attempts have been made to achieve prolonged local tumor control after radiation using surgery[6,13,15,17,18,20,22)], radiation sensitizers[16,19,23)], boost techniques[24,25)], and accelerated radiotherapy[5,6)]. One study evaluating a combination of accelerated radiotherapy and subsequent exenteration of the nasal cavity reported a median survival time of 47.7 months; however, severe late side effects including chronic rhinitis, osteoradionecrosis, and vision loss were not uncommon[6)].

Hypofractionated radiation protocols have advantages of lower cost and lesser anesthetic requirements for each radiotherapy session, compared to more finely fractionated protocols. Thus, hypofractionated radiation protocols have been evaluated in multiple studies[8,10,12,14,17]. This study aimed to evaluate the hypothesis that hypofractionated radiotherapy followed by surgical debulking of canine nasal tumors would lead to an improved control of the local tumor.

Materials and Methods

Between May 2009 and December 2014, 18 dogs with intranasal tumors were treated using hypofractionated radiotherapy protocols followed by surgical resection. Informed consent was obtained from the owners of the animals. Information was obtained from medical records, telephone interviews with the owners, or the referring veterinarians. Evaluated variables included breed, sex, age, body weight, clinical signs, duration of clinical signs prior to presentation (months), tumor stage including the tumor and lymph node involvement, distant metastasis staging (TNM), and histological tumor type. Collected data regarding the treatments included the overall radiation treatment time, radiation dose per fraction, total dose, duration between the last radiation treatment and surgery, and other details regarding surgery (whether bone was removed, bone flaps were used, and presence of microscopic or macroscopic residual tumors after surgery). Collected data regarding the follow-ups included complications, local tumor recurrence, time from the completion of radiotherapy to local tumor recurrence, and the duration of the follow-up period. Progression-free survival was defined as the time from the completion of radiation treatment till the recurrence was first detected or suspected. No dog in this study was treated with either chemotherapy or non-steroidal anti-inflammatory drugs.

The treatment schedule was as follows. Computed tomography (CT) was performed in all dogs prior to radiotherapy to determine the size, location, and extent of the tumor. A CT scan was performed 1–2 months after the completion of radiotherapy (six cases in total), and residual tumors were resected, as described in the study by Adams et al.[6]. However, based on the study published by the authors, only 10% of the dogs treated with hypofractionated radiotherapy alone achieved a complete response (i.e., complete disappearance of the gross disease) [12]. Therefore, in the subsequently treated eight cases, residual tumor resection was performed immediately after the last radiotherapy session without waiting for one month after radiotherapy. CT scans were acquired immediately before and after debulking surgery.

Intranasal tumors were classified using the TNM system and the tumor staging criteria defined by the World Health Organization[26] and Adams et al.[5] based on CT imaging. Survival time was calculated from the completion of radiation treatment to the time of death. Complications were graded using the toxicity criteria described by the Veterinary Radiation Therapy Oncology Group (VRTOG) [27], and the Clavien-Dindo classification (JCOG) [28].

A three-dimensional computer planning software (ARCS-III; Nihon Denshi Ohyo Co., Ltd., Tokyo, Japan) was used for the radiotherapy of 11 dogs. The radiotherapy software was replaced by another software package (XiO, Elekta Co., Ltd., Tokyo, Japan) used to plan the treatment for seven dogs. The dose was prescribed for the entire planning target volume, defined as the gross tumor volume (GTV) with at least 1 cm isotropic margins around the GTV. A 4-MV photon beam generated by a linear accelerator (Mevatron; Toshiba, Tokyo, Japan) was used for 11 dogs, and 6-MV photon beams generated by another linear accelerator (Primus, Toshiba, Tokyo, Japan) were used for seven dogs. A commercially available 0.5-cm-thick bolus material (MTCB 410 S, CIVCO Medical Solutions, Kalona, IA, USA) was used for all dogs, except for one with a deeply seated tumor not requiring a bolus[12].

Prior to surgical debulking, the rostral and the caudal extents of the tumor were evaluated based on the distance from the rostral end of the nasal planum on the CT images. A skin incision was made 5 mm from the rostral and caudal extents of the tumor. A chisel was used to remove the bone and to expose the nasal cavity. In case of replacement of the removed bone, it was removed with the attached periosteum, and after the surgical procedure, the periosteum

was sutured restoring back the bone. In case of permanent removal of the bone, the periosteum was separated from the bone and sutured after the surgical procedure. The bone and associated periosteum were permanently removed when the tumor had eroded through the bone. Tumor removal was performed using suction and curettage. The tumor with the surrounding mucous membrane were removed until the bone was exposed. The intact bone flap was then returned or removed, and any visible tumor tissue invading the bone was also resected. The bone flap with the attached periosteum was sutured using 4-0 absorbable material (Maxon, Covidien, Dublin, Ireland). The skin incision was closed with subcuticular sutures using 5-0 absorbable material with simple interrupted sutures using 4-0 non-absorbable material (Monosof, Covidien, Dublin, Ireland).

The survival analysis was performed using the Kaplan-Meier method, and a log-rank test was used to assess progression-free survival time and factors related to outcome, including age, body weight, duration of clinical signs prior to presentation, tumor stage, tumor type (carcinoma vs. sarcoma), timing of the surgery relative to radiotherapy (during radiotherapy vs. post-radiotherapy), presence of macroscopic tumor after surgery (yes or no), and recurrence. Statistical significance was set at $p < 0.05$, and statistical analyses were conducted using a computer software program (JMP version 8.02, SAS Institute, Inc., Cary, NC, U.S.A.).

Results

The characteristics of the dogs are shown in Table 1. There were 5 neutered males, 3 intact males, 8 neutered females, and 2 intact females. The mean age was 12 years (range, 8–14 years), and the mean body weight was 18.0 kg (range, 6.7–40.2 kg). The clinical signs included epistaxis (n = 11), sneezing and/or nasal discharge (n = 10), and facial deformity (n = 9). The median duration of the clinical signs prior to presentation was 2 months (range, 1–6 months). A total of 4 dogs were classified with T1, one with T2, and the remaining 13 with T3 tumors. Neither lymph node involvement nor distant metastasis was noted in any dog at the time of staging. The tumors were classified as stage I in 4 dogs, stage II in one, stage III in 5, and stage IV in 8 dogs. There were 12 carcinomas (seven adenocarcinomas, 2 transitional

Table 1. Characteristics of the dogs

No.	Breed	Clinical signs	Duration of clinical signs prior to presentation (months)	TNM classification[26]	Tumor stage[5]	Tumor type
1	Shetland Sheepdog	Ep, SD, FD	1	T3N0M0	III	CA
2	Pembroke Welsh Corgi	FD	6	T3N0M0	III	AC
3	Labrador Retriever	SD, FD	2	T3N0M0	IV	CSA
4	Shiba Inu	Ep, FD	2	T3N0M0	IV	FSA
5	German Shepherd	Ep, SD	2	T1N0M0	I	AC
6	Pembroke Welsh Corgi	Ep, FD	1	T3N0M0	III	OSA
7	Miniature Dachshund	Ep, FD	2	T3N0M0	IV	AC
8	Labrador Retriever	Ep	2	T3N0M0	IV	TC
9	Labrador Retriever	FD	1	T3N0M0	III	OSA
10	Pomeranian	SD	1	T3N0M0	III	TC
11	Golden Retriever	Ep	1	T1N0M0	I	CA
12	Labrador Retriever	Ep, SD	2	T1N0M0	I	AC
13	Pembroke Welsh Corgi	Ep, SD, FD	2	T3N0M0	IV	AC
14	Shih Tzu	SD	1	T2N0M0	II	SCC
15	Pug	Ep, SD	2	T1N0M0	I	AC
16	Border Collie	FD	1	T3N0M0	IV	AC
17	Golden Retriever	SD	5	T3N0M0	IV	OSA
18	Pembroke Welsh Corgi	Ep, SD	1	T3N0M0	IV	CSA

Ep, Epistaxis; SD, sneezing and nasal discharge; FD, facial deformity
AC, adenocarcinoma; CA, carcinoma; SCC, squamous cell carcinoma; TC, transitional carcinoma; OSA, osteosarcoma; CSA, chondrosarcoma; FSA, fibrosarcoma

Table 2. Summary of the treatment methods and outcomes

No.	Total dose / fractions	Timing of surgery relative to RT	Bone flap	Complications (except for VRTOG classification)	Macroscopic tumor remained after surgery	Recurrence	DFI (months)
1	32 Gy/4	1.5 months post-RT	Removed	ND	No	-	> 26
2	28 Gy/4	2 months post-RT	Removed	Abscess (frontal sinus)	No	-	39
3	28 Gy/4	1.5 months post-RT	Removed	Rhinitis	Yes	+	2
4	28 Gy/4	1 month post-RT	Removed	Subcutaneous emphysema	Yes	+	3
5	28 Gy/4	1.5 months post-RT	Returned	Chronic rhinitis	No	-	16
6	28 Gy/4	Last RT (4th)	Removed	Subcutaneous emphysema	Yes	+	3
7	28 Gy/4	Last RT (4th)	Removed	Subcutaneous emphysema	No	+	2
8	28 Gy/4	Last RT (4th)	Returned	Bone necrosis, fistulae, rhinitis	No	+	1
9	28 Gy/4	Last RT (4th)	Removed	ND	Yes	+	2
10	28 Gy/4	Last RT (4th)	Returned	Rhinitis	Yes	+	3
11	28 Gy/4	Last RT (4th)	Returned	Bone necrosis, fistulae, chronic rhinitis	No	-	> 21
12	28 Gy/4	Last RT (4th)	Removed	ND	No	+	5
13	28 Gy/4	Last RT (4th)	Removed	Subcutaneous emphysema, rhinitis	No	+	3
14	28 Gy/4	1 month post-RT	Removed	Chronic rhinitis	No	-	> 12
15	28 Gy/4	1 month post-RT	Removed	Rhinitis	No	-	36
16	28 Gy/4	Last RT (4th)	Removed	Rhinitis	No	+	11
17	28 Gy/4	1 month post-RT	Removed	Chronic rhinitis	No	-	25
18	28 Gy/4	Last RT (4th)	Removed	Rhinitis	No	+	7

ND, not detected; PFS, progression-free survival; RT, radiotherapy

carcinomas, 2 carcinomas, and 1 squamous cell carcinoma) and 6 sarcomas (3 osteosarcomas, 2 chondrosarcoma, and 1 fibrosarcoma). No dog had submucosal involvement.

The hypofractionated radiotherapy consisted of 4 weekly treatments using 7–8 Gy per fraction (median, 7 Gy) for a total period of 4 weeks. The median total dose was 28–32 Gy (median, 28 Gy). Surgical resection was performed after the completion of hypofractionated radiotherapy in 8 dogs or immediately after the last session of hypofractionated radiotherapy in 10 dogs. The tissue dorsal to the nasal cavity was removed in 14 of 18 dogs, with tumors involving subcutaneous tissue in this area to expose the nasal cavity. An intact bone flap was returned and sutured in 4 dogs; however, removed in the remaining dogs because of high morbidity (2 of the 4 sutured dogs returned and developed nasocutaneous fistulae). All macroscopic (visible) tumors were removed by surgery in 13 dogs (Table 2); however, macroscopic residual tumors were present in the remaining 5 dogs, when the surgical procedure was completed, because the tumors extended widely and were not resected completely.

All complications were limited to the skin and eyes. Observed acute effects included hair loss (n = 5, grade I) and mild conjunctivitis (n = 5, grade I). Late side effects included keratoconjunctivitis sicca (n = 5, grade I), cataract (n = 3, grade II), and rhinitis (n = 11). In the 11 dogs that developed rhinitis, four developed chronic rhinitis, although the symptoms were alleviated in all dogs using intermittent antibiotic drugs (grade II). Nasocutaneous fistulae developed in both dogs with infections of the bone flap (cases 2 and 8, grade IIIb). Table 2 summarizes the variables related to the treatments and outcomes.

Recurrence was detected based on a CT scan in 6 dogs, head radiographs in one, development or progression of facial deformity in four, by histopathology in four, and by cytology in one dog. Among the 11 dogs that developed recurrence, one was at stage I, 3 were at stage III, and the remaining 7 were at stage IV. All dogs with macroscopic residual disease when the surgical procedure was completed, developed recurrence. The median time to recurrence was 3 months (range, 1–5 months). The median progression-free survival and overall survival were 6, and 10 months (Figs. 1 and 2). The median overall survival of dogs with stage I, II, and III disease was 26 months.

Univariate analysis indicated macroscopic tumor resection after surgery ($p = 0.008$), and the timing of surgery ≥

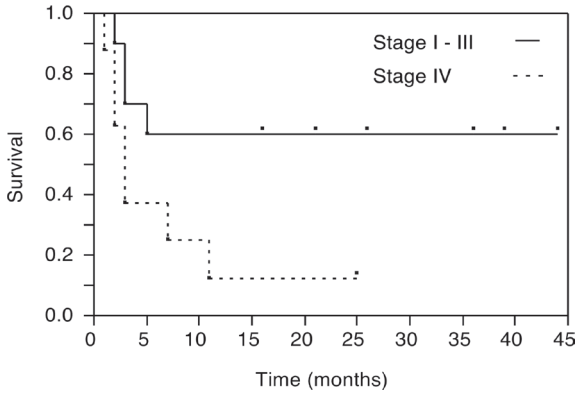

Fig. 1. Progression-free survival curve of hypofractionated radiotherapy following marginal tumor resection in dogs with stage I – III, and IV intranasal tumors. The median progression-free survival time of stage IV was 3 months, and that of stage I – III was not reached.

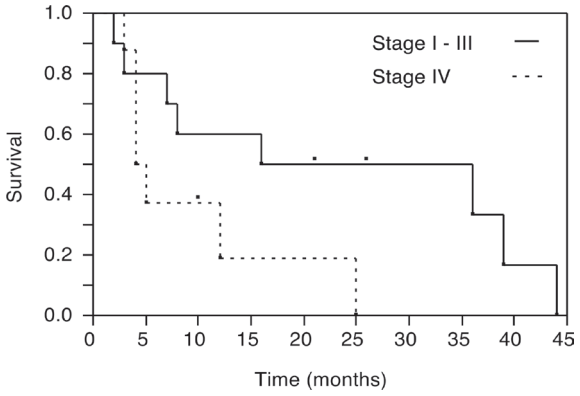

Fig. 2. Kaplan-Meier survival curve of hypofractionated radiotherapy following marginal tumor resection in dogs with stage I – III, and IV intranasal tumors. The median overall survival time of stage I – III, and IV was 26, and 4.5 months.

one month post-radiotherapy (p = 0.011) were potentially associated with a favorable survival time and tumor stage (I–III vs. IV; p = 0.043, Fig. 1).

Discussion

The results of this study suggest that a combination of hypofractionated radiotherapy followed by surgical resection for dogs with intranasal tumor may lead to longer tumor control compared to hypofractionated radiotherapy alone, especially for tumors in the early stages (stages I, II, and III). The median overall survival was 26 months in the early stages (stages I, II, and III). Hence, most dogs at stage IV did not benefit from surgical debulking post-radiotherapy. However, the infection rate in this combination treatment was high.

The combination of radiotherapy and surgery was proposed for dogs with intranasal tumors[6,13]. A study evaluated dogs with intranasal tumor that underwent surgical resection followed by radiotherapy (41.8–54 Gy/10–12 fractions). The median survival time in the study was 15 months[13]. In another study by Adams et al.[6], radiotherapy was followed by surgery and the median survival time was 47.7 months. In our study, hypofractionated radiotherapy followed by surgical debulking resulted in a median survival of 26 months for early-stage disease (stages I, II, and III). Consistent with Adams et al.[6], the results of this study suggested that radiotherapy before surgery resulted in better outcomes than radiation after surgery.

A local recurrence of intranasal neoplasia in six of 13 dogs was reported 3 to 48 months after treatment[6]. In our study, of 11 dogs with recurrence, three had stage III disease with orbit invasion and seven had stage IV disease at initial presentation. In the remaining 7 dogs, the visible tumor was completely removed, leaving no bulky disease. Of these 7 dogs, 3 had stage I, 1 had stage II, 2 had stage III with only subcutaneous involvement, and one had stage IV disease. Therefore, early recurrence is more likely in dogs with advanced stage disease. In our study, recurrence occurred within 5 months of the completion of radiotherapy. The period prior to recurrence was shorter than that observed by Adams et al.[6] and may have resulted from the lower total dose of radiotherapy used in our study.

Severe late radiation side effects in dogs with intranasal tumors treated by hypofractionated radiotherapy, including loss of vision and oronasal fistulae, were reported in several studies[10,12,14]. Various complications in dogs treated with radiotherapy followed by surgery included chronic rhinitis in five dogs, osteosarcoma of the maxilla 5 years after radiotherapy in one, and loss of vision within the radiation field in 3 dogs[6]. It is well-known that the surgical complication rate is higher if the surgery is performed in previously

irradiated areas[29]. In our study, infection of bone flaps in 2 dogs resulted in nasocutaneous fistulae (grade IIIb). Currently, replacement of the incised bone after debulking nasal tumors is not advocated because 2 of the 4 dogs with replaced bone flaps in this study got infected followed by the development of nasocutaneous fistulae. The incidence of rhinitis was high. Removing the mucous membrane inside the nasal passage may predispose dogs to rhinitis. However, all the VRTOG-classified side effects were mild to moderate, probably due to the low total dose (28 Gy) of radiotherapy. These data demonstrate that the described combination treatment could lead to chronic infection and nasocutaneous fistulae.

Chemoradiotherapy is effective for human head and neck cancer[30,31] and was superior to radiotherapy alone after surgery in advanced squamous cell carcinoma of the head and neck in human[30]. Chemoradiotherapy using cisplatin, carboplatin, and gemcitabine was used in veterinary medicine; however, the survival time with these chemotherapeutic agents were similar to that with radiotherapy alone[1]. In this study, a hypofractionated radiotherapy protocol without chemotherapeutic drug was adopted. However, chemoradiotherapy might be an alternative modality to improve the survival time because of the low total dose of radiotherapy in this study.

There were several limitations to this study; a small sample size, various histological tumor types, and varied treatment protocols. A negative predictor of the histologic subtype was carcinoma, particularly squamous cell carcinoma or undifferentiated carcinoma[1]. However, there was no significant difference in the survival time between carcinoma and sarcoma. Tumor recurrence in long-term survivors is uncertain. There was also a possibility that the survivors in this study may develop a radiation-induced tumor in the future. The timing of surgery ≥ one month post-radiotherapy yielded a significantly improved survival rate ($p = 0.011$), which may be an unintended consequence in favorable cases.

Nevertheless, hypofractionated radiation followed by surgery may significantly improve the survival time in dogs with early-stage disease (stages I, II, and III) compared to hypofractionated radiation alone. Therefore, microscopic residual tumor resection should be considered 1 month after completion of hypofractionated radiotherapy in dogs with stage I – III intranasal tumors.

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