



NOTE

Internal Medicine

Prognostic significance of midline shift of the olfactory or frontal lobes of the brain in canine nasal carcinomas treated by palliative radiotherapy: a pilot study

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ABSTRACT. Canine nasal carcinomas are often treated with radiotherapy. Presence of lysis of the cribriform plate by tumor invasion (stage 4 by modified Adams's staging system) is a well-known prognostic factor. In this study, dogs with stage 4 disease were divided into two subgroups based on the presence or absence of midline shift of the olfactory or frontal lobes of the brain (Stage 4a: without presence of midline shift. Stage 4b: with midline shift). The median survival time of dogs with midline shift was significantly shorter than that of dogs without midline shift (64 vs. 208 days). Our results indicate that the finding of a midline shift might have a prognostic significance in dogs with nasal carcinoma treated with radiotherapy.

KEY WORDS: dog, nasal carcinoma, prognosis, radiotherapy

Nasal tumors account for 1–2% of all reported canine neoplasms [9, 10]. Carcinomas comprise two-thirds of canine intranasal tumors and are characterized by progressive local invasion and low metastatic rate [15]. Without treatment, the median survival time (MST) of dogs with nasal tumors has been reported to be 3.1 months [13]. The most common therapy for these carcinomas is high-voltage radiotherapy using megavoltage x-rays; surgery alone has proven to be of little benefit in prolonging survival time [13]. The MST of dogs treated with radiotherapy is 4.9–19.7 months [1, 3–6, 11].

Studies have reported many prognostic factors for canine nasal tumors including the presence of epistaxis, histological tumor type, age, and clinical stage [1, 8, 13]. For clinical staging, several methods have been suggested. Application of the World Health Organization staging method to canine nasal tumors is known to have no prognostic relevance [7, 14]. More recently, Adams *et al.* have advocated a new staging method that showed an association between clinical stage and prognosis [1]. This classification showed that the MST of the dogs with stage 4 disease (tumor with cribriform plate destruction) was the shortest compared with that for other stages (e.g. stage 1–23.4 months vs. stage 4–6.7 months) after radiotherapy. Therefore, a modified Adams's classification has often been used in previous studies. On the other hand, Agthe *et al.* reported that caudal nasal recess involvement, meningeal hyperintensity, and intracranial tumor extension tended to be associated with shorter survival, as assessed by magnetic resonance imaging (MRI) [2]. In this way, cribriform plate destruction alone may not always predict survival time for dogs with advanced nasal tumors. Based on these findings, we investigated factors influencing survival in dogs with stage 4 disease. We focused on the association between a midline shift of the olfactory or frontal lobes of the brain, as detected by computed tomography (CT), and survival time after radiotherapy.

This was a retrospective observational study. The medical records of dogs with stage 4 nasal carcinoma treated at the Veterinary Medical Center of Osaka Prefecture University between 2014 and 2017 were retrospectively reviewed for cases that had received palliative radiotherapy. Dogs that had concurrently received surgery or re-radiotherapy were excluded from this study.

Complete blood cell counts, serum biochemical profile, and histopathological diagnosis before radiotherapy had been performed on all subjects. Prior to radiotherapy, CT of the head was performed on the dogs when properly positioned and immobilized with a bite block and a vacuum bag. As shown in Fig. 1, all patients could be divided into 2 groups according to the presence or absence of a midline shift of the olfactory or frontal lobes of the brain as evidenced on CT (stage 4a, without presence of midline shift; stage 4b, with midline shift). We defined the midline shift as a >2 mm departure from a line connecting the dorsal and ventral

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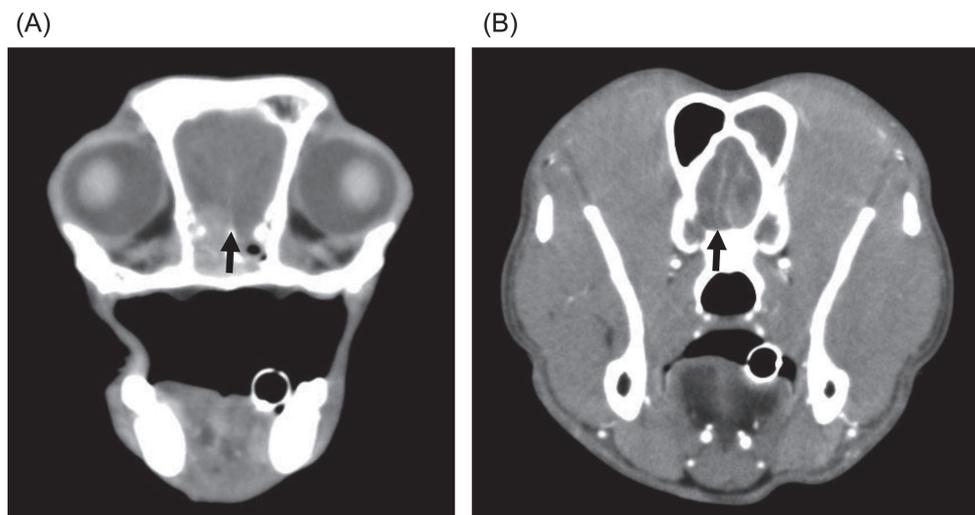


Fig. 1. Representative images of stage 4a (A) and stage 4b (B) in the transverse plane of contrast-enhanced CT. Arrows indicates midline of olfactory bulb (B) and frontal lobe (A) of the brain.

falx cerebri. Further, the regional lymph node status was evaluated by performing a CT scan. Information about the dogs was obtained from medical records or telephone interviews with the owner or referring veterinarian including their breed, age, clinical symptoms, survival time, and cause of death.

All dogs had received 3D-conformal radiation therapy: 4 doses of 8–9 Gy megavoltage radiotherapy given at 7-day intervals by a 4 MV X-ray linear accelerator (PRIMUS; Toshiba Medical Systems Corp., Tochigi, Japan). Individualized treatment plans were generated with 3D treatment planning software (XiO, Elekta Japan, Tokyo, Japan). The gross tumor volume (GTV) was contoured using 2 mm slice thickness CT image sets and included contrast-enhancing mass containing discharge and the brain area where the tumor was suspected to have invaded. Planning target volume (PTV) included the region 0.3–0.5 cm outside the GTV. The prescription point of radiation dose was set at the isocenter, covering over 80% of the PTV. Wedges were used, if necessary, for a homogenous dose distribution.

Survival analysis was performed using commercial statistical software GraphPad Prism 7 (GraphPad software, La Jolla, CA, U.S.A.). Survival was defined as the interval between the date of start of radiotherapy and time of death. Dogs that remained alive at the end of the study, died from some unrelated cause or were euthanized were censored in the survival analysis. The Kaplan-Meier method was used to prepare overall survival (OS) curves, while the log-rank test was used to compare time-to-event distributions. A *P*-value of <0.05 was considered significant for all analyses.

Sixteen dogs were included in this study. There were 8 males (of which 3 had been castrated) and 8 females (all of which had been spayed). Their ages ranged from 7 to 17 years (median, 11.5 years). There were 2 mixed-breed dogs and the following 14 pure-breed ones: Shiba (*n*=4), Miniature Dachshund (*n*=3), Chihuahua (*n*=2), Welsh Corgi (*n*=1), Shetland Sheepdog (*n*=1), Maltese (*n*=1), Pug (*n*=1), and Sealyham Terrier (*n*=1). Tumor types included adenocarcinoma (*n*=13), transitional nasal carcinoma (*n*=1), undifferentiated carcinoma (*n*=1), and carcinoma (*n*=1). Eight dogs had tumor stage 4a and eight had stage 4b. Two dogs received chemotherapy with toceranib (Palladia®, Zoetis, Tokyo, Japan) after radiotherapy. The characteristics of all patients are summarized in Table 1.

Clinical symptoms observed before radiotherapy included epistaxis (*n*=14), dyspnea (*n*=7), facial deformity (*n*=6), neurologic abnormality (seizure, *n*=4; head tilt, *n*=1), and lymphadenopathy (*n*=7). Cytological or histological examination of lymph nodes was not performed.

Of the 16 dogs, 2 were alive at the end of the study. Thirteen dogs died due to tumor related or other causes and 1 dog was euthanized due to tumor progression. The MST for all dogs was 120.5 days (range, 38–476 days; Fig. 2), which was shorter than that reported in a previous study by Maruo *et al.*, in which the MST of the dogs with cribriform plate destruction was 163 days after treatment with the same radiotherapy protocol (median total dose was 32 Gy) [11]. We hypothesized that the reason for this short time survival was due to a difference of severity in stage 4. Another report indicated that tumor extension into the cranium was associated with shorter survival in dogs with nasal tumors treated with radiotherapy [2]. Thus, we focused on the midline shift of the olfactory bulb or frontal lobes of the brain. The MST of dogs with stage 4a (208 days) was significantly longer than that of those with stage 4b (64 days; Fig. 3 and Table 2). The results allowed us to consider that the proportion of stage 4b (8 of 16 dogs) was responsible for the overall shorter MST in this study.

The known prognostic factors for nasal carcinoma include tumor type, stage, epistaxis, age, regional lymph node or pulmonary metastasis, and facial deformity [1, 7, 8, 12, 13]. However, there was no significant difference in the MST based on pre-therapy clinical symptoms (epistaxis, dyspnea, facial deformity, neurologic abnormality, and lymphadenopathy; Table 2). We did not evaluate for metastasis to regional lymph nodes in all cases, although there were none with pulmonary metastasis, which had been

Table 1. Patient information

No.	Sex	Age	Breed	Diagnosis	Clinical stage	Survival time (day)	Adjuvant therapy	Outcome	Cause of death
1	SF	17	Miniture Dachshund	Adenocarcinoma	4a	38	None	Death	Tumor related
2	SF	11	Welsh Corgi	Adenocarcinoma	4a	171	None	Death	Euthanasia
3	SF	12	Shiba	Adenocarcinoma	4a	208	None	Death	Tumor related
4	CM	13	Shiba	Transitional carcinoma	4a	111	None	Death	Unknown
5	M	12	Chihuahua	Undifferentiated carcinoma	4a	476	None	Alive	
6	CM	12	Mixed	Adenocarcinoma	4a	288	Toceranib	Death	Tumor related
7	SF	13	Shetland Sheepdog	Adenocarcinoma	4a	202	Toceranib	Death	Arrythmia
8	M	10	Maltese	Adenocarcinoma	4a	204	None	Alive	
9	SF	11	Mongrel	Adenocarcinoma	4b	49	None	Death	Tumor related
10	SF	10	Miniture Dachshund	Adenocarcinoma	4b	55	None	Death	Tumor related
11	M	7	Pug	Adenocarcinoma	4b	129	None	Death	Tumor related
12	M	12	Shiba	Adenocarcinoma	4b	154	None	Death	Tumor related
13	M	14	Shiba	Adenocarcinoma	4b	56	None	Death	Tumor related
14	SF	10	Miniture Dachshund	Adenocarcinoma	4b	112	None	Death	Tumor related
15	CM	11	Chihuahua	Adenocarcinoma	4b	58	None	Death	Tumor related
16	SF	11	Sealyham Terrier	Carcinoma	4b	70	None	Death	Tumor related

SF, spayed female; CM, castrated male; M, male.

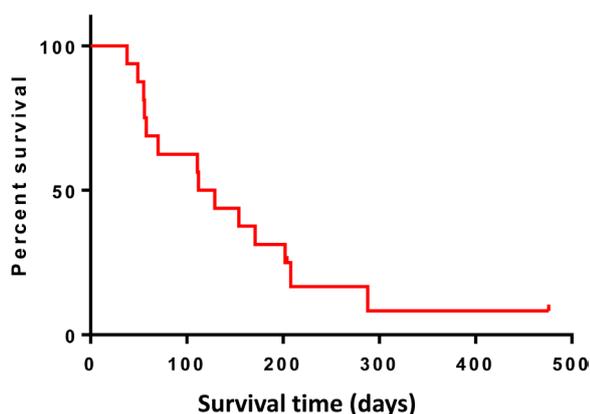


Fig. 2. Kaplan-Meier survival curve of survival time for 16 dogs with nasal tumor in stage 4. In our study, the MST was 120.5 days.

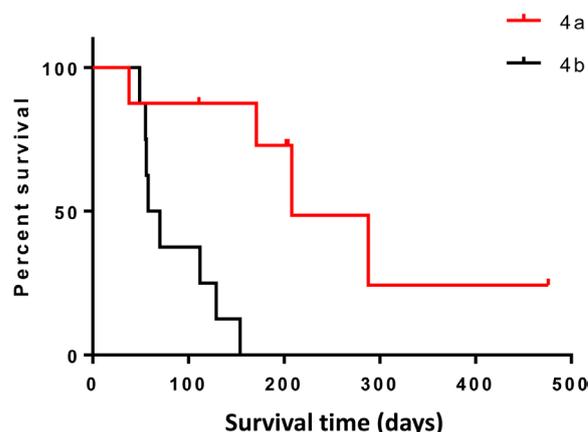


Fig. 3. Kaplan-Meier survival curves of the dogs with stage 4a and stage 4b tumors. The red line is stage 4a with an MST of 208 days (n=8), and the black line, stage 4b with an MST of 64 days (n=8).

Table 2. Median survival times for all dogs included in the study

Characteristic		Number with characteristic (%)	Median survival time (day)	P value
Midline shift	Yes	8 (50)	64	0.0015
	No	8 (50)	208	
Epistaxis	Yes	14 (88)	141.5	0.1517
	No	2 (12)	80.5	
Dyspnea	Yes	7 (44)	204	0.3794
	No	9 (56)	70	
Facial deformity	Yes	6 (38)	181	0.2163
	No	10 (62)	111.5	
Neurologic abnormality	Yes	5 (31)	112	0.4587
	No	11 (69)	129	
Lymphadenopathy	Yes	7 (44)	154	0.4533
	No	9 (56)	111	

assessed by CT.

The major limitation of this study was the small sample set, which possibly reflected a statistical error. Despite these limitations, this study suggests that dogs with stage 4b disease have a short survival period (MST, 64 days). These results indicate that radiation therapy for dogs with stage 4b tumors might be able to improve their clinical symptoms, but not prolong survival time. Further studies with a larger population are needed to validate the prognostic significance of a midline shift in cases with stage 4 nasal tumors.

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