Internal medicine, note

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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Running head: PROGNOSIS OF CANINE ADVANCED NASAL TUMOR
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 days 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 WORD: 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 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 Corporation, 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, USA). 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 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.

Acknowledgments

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References

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**Figure legends**

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.

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 1. Patients’ information.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Breed</th>
<th>Diagnosis</th>
<th>Clinical stage</th>
<th>Survival time (d)</th>
<th>Adjuvant therapy</th>
<th>Outcome</th>
<th>Cause of death</th>
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<tbody>
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<td>1</td>
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<td>Miniature Dachshund</td>
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<td>4a</td>
<td>38</td>
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<td>Death</td>
<td>Tumor related</td>
</tr>
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<td>11</td>
<td>Welsh Corgi</td>
<td>Adenocarcinoma</td>
<td>4a</td>
<td>171</td>
<td>None</td>
<td>Death</td>
<td>Euthanasia</td>
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<tr>
<td>3</td>
<td>SF</td>
<td>12</td>
<td>Shiba</td>
<td>Adenocarcinoma</td>
<td>4a</td>
<td>208</td>
<td>None</td>
<td>Death</td>
<td>Tumor related</td>
</tr>
<tr>
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<td>13</td>
<td>Shiba</td>
<td>Transitional carcinoma</td>
<td>4a</td>
<td>111</td>
<td>None</td>
<td>Death</td>
<td>Unknown</td>
</tr>
<tr>
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<td>M</td>
<td>12</td>
<td>Chihuahua</td>
<td>Undifferentiated carcinoma</td>
<td>4a</td>
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<td></td>
</tr>
<tr>
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<td>CM</td>
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<td>Mixed</td>
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<td>288</td>
<td>Toceranib</td>
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<td>Death</td>
<td>Arrhythmia</td>
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<td>M</td>
<td>10</td>
<td>Maltese</td>
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<td>4a</td>
<td>204</td>
<td>None</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SF</td>
<td>11</td>
<td>Mongrel</td>
<td>Adenocarcinoma</td>
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<td>49</td>
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<td>Tumor related</td>
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</tr>
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<td>M</td>
<td>7</td>
<td>Pug</td>
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<tr>
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<td>M</td>
<td>12</td>
<td>Shiba</td>
<td>Adenocarcinoma</td>
<td>4b</td>
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<td>M</td>
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<td>Shiba</td>
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</table>

SF, spayed female; CM, castrated male; M, male.
Table 2. Median survival times for all dogs included in the study.

<table>
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<th>Characteristic</th>
<th>Number with characteristic (%)</th>
<th>Median survival time (d)</th>
<th>p value</th>
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<td>Midline shift</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (50)</td>
<td>64</td>
<td>0.0015</td>
</tr>
<tr>
<td>No</td>
<td>8 (50)</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (88)</td>
<td>141.5</td>
<td>0.1517</td>
</tr>
<tr>
<td>No</td>
<td>2 (12)</td>
<td>80.5</td>
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<tr>
<td>Dyspnea</td>
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<td></td>
<td></td>
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<tr>
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<td>7 (44)</td>
<td>204</td>
<td>0.3794</td>
</tr>
<tr>
<td>No</td>
<td>9 (56)</td>
<td>70</td>
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<tr>
<td>Facial deformity</td>
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<td></td>
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<td>Yes</td>
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<td>181</td>
<td>0.2163</td>
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<td>10 (62)</td>
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</table>
Fig. 1

(A) (B)
Fig. 2

Percent survival vs. survival time (days)
Fig. 3

The graph shows the percent survival over survival time in days. Two lines are depicted, labeled 4a and 4b. The y-axis represents percent survival, ranging from 0 to 100, while the x-axis represents survival time in days, ranging from 0 to 500.