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Treatment outcomes of canine nasal tumor irradiation

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Original Article

Treatment outcomes of canine nasal tumor irradiation

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Abstract

This study aimed to determine the treatment response of canine nasal tumor treated with only linear accelerated radiation therapy (LINAC) using volumetric measurement criteria at Kasetsart University Veterinary Teaching Hospital between May 2013 and August 2015. Medical records of the patients including age, breed, sex, histopathological diagnosis, clinical stage, types of radiation therapy and complications of treatment were recorded. All 20 dogs were irradiated with total dose ranging from 36 to 54 Gray (Gy). Computed tomography was performed with all dogs before and three months after treatment in order to evaluate tumor volume change. Results revealed that median survival time for all dogs was 383 days (95%CI 214.69-551.31) and median progression free was 384 days (95%CI 240.94-527.06). Considering tumor volume change, six dogs (30%) were classified as partial response at 3 months after radiation therapy, while 14 dogs (70%) were classified as stable disease. In addition, considering variables associated with survival time analyzed by log-rank test, it was found that age and volumetric measurement response correlated with survival time statistically significantly ($P<0.05$).

Keywords: nasal tumor, radiotherapy, survival time, volumetric measurement

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Introduction

In dogs, intranasal tumor accounts for approximately 1-2% of all tumors. The average age of dog found with such tumor is approximately 9 years old (Turek and Lana, 2007). Common clinical signs of this tumor include epistaxis, sneeze and dyspnea. In addition, neurological disorders occur in some cases because the tumor occasionally invades the brain (Maruo et al., 2011). Approximately two thirds of canine intranasal tumor cases are diagnosed as carcinomas. The rest are malignant mesenchymal tumors (e.g. osteosarcoma, chondrosarcoma, and fibrosarcoma), while round cell tumors (e.g. lymphoma, mast cell tumor, and transmissible venereal tumor) and other malignant tumors are rare in the intranasal region.

The optimal treatment of nasal tumor is controversial. The existence of vital organs such as the brain or eyes and the invasion of the tumor to skull base often result in difficulty in totally removing the intranasal tumor. Without treatment, the median survival time is not more than 4-6 months. Generally, nasal exenteration can be performed by two approaches: dorsal rhinotomy and ventral approach through hard palate. However, it is still difficult to remove all tumors because by the time clinical signs are present the tumor usually already invades neighboring tissues (Malinowski, 2006). Laing and Binnington (1988) reported that the median survival times of dogs treated by only surgery were 11 months and 3 months for unilateral and bilateral nasal tumors, respectively. A recent study has demonstrated that dogs treated with radiotherapy followed by nasal surgery had significantly longer survival time (47.7 months) than those treated with radiotherapy alone (19.7 months) even though serious treatment side effects occurred more frequently in the combined radiotherapy-surgery group (Adams et al., 2005). Chemotherapy has limited efficacy and does not improve survival time of affected dogs. Langova et al. (2004) studied the outcome of canine nasal tumor treatment with doxorubicin and carboplatin combined with piroxicam and reported that four of eight dogs had complete remission of nasal tumors from CT scan and two dogs had partial remission with no report of survival time.

Nowadays, radiation therapy is the treatment of choice for intranasal tumor in dogs. The main advantage of radiotherapy for nasal tumor is the preservation of organs and their functions by delivering enough total doses to the tumor while sparing the adjacent critical normal structure from excessive dose. Various radiation treatment protocols in veterinary medicine have been reported. The definitive therapy protocol uses a small dose (such as 3 Gy or 4.2 Gy) per fraction daily or on alternate days to a relatively high total dose (42 to 60 Gy) (Moore, 2002). Median survival time of dogs treated with the definitive therapy protocol is 450 days (Lana et al., 2004; Adams et al., 2005). Besides, dogs with metastatic tumor through the cribiform plate possess median survival time of 200 days (Kondo et al., 2008; Adams et al., 2009; Mason et al., 2013). The palliative radiation protocol uses a higher dose per fraction weekly in order to increase quality of dog life, not for long-term tumor control. Sones et al. (2013) reported 305 days of median survival time from 16 canine nasal sarcoma cases which underwent 6 Gy per fraction weekly to total dose less than 36 Gy protocol.

Survival time is the most important outcome of cancer treatment. However, other tumor response assessments such as quality of life and tumor shrinkage are clinically meaningful changes produced by treatment. At the present time, tumor response assessment is based primarily on changes in tumor size as measured by computed tomography or CT (Fiteni et al., 2014). Various criteria have been used to evaluate treatment response. The first well-known is the World Health Organization (WHO) criteria, which apply bidimensional tumor measurement (World Health Organization, 1979). The second is the response evaluation of solid tumor (RECIST) criteria, which apply unidimensional tumor measurement (Eisenhauer et al., 2009). Both WHO and RECIST criteria were originated from round-shaped tumor, but most nasal tumors are in irregular shapes (James et al., 1999). During the past few years, the advance in diagnostic imaging modality has made volumetric measurement more effective for the treatment response measurement of irregular-shaped tumor than other criteria (King et al., 2007). Therefore, the purpose of this study was to determine the treatment response of canine nasal tumor treated with only linear accelerated radiation therapy (LINAC) using the volumetric measurement criteria. Clinical outcomes such as median survival time, progression free survival time, complication and potential prognostic factors were also evaluated.

Materials and Methods

Twenty dogs with histologically confirmed intranasal tumor were included in this study. All dogs were treated with radiation therapy at Kasetsart University Veterinary Teaching Hospital (KUVTH) between May 2013 and April 2015. Clinical data of each dog including age, breed, sex, clinical signs involved in nasal tumor before treatment, duration from presence of clinical signs to beginning of treatment protocol, histological type, TNM, clinical staging, complete blood count, serum alkaline phosphatase, creatinine, radiation protocol and side effects from radiation therapy were recorded.

Before radiation treatment, all dogs underwent CT scan (Optima CT660, GE Healthcare, Wisconsin, USA) for tumor staging based on Adams' classification with slight modifications (Adams et al., 2009) and again at three months after treatment in order to assess tumor treatment response, which was evaluated by measuring volume of tumor before and after radiation treatments. Tumor burden was manually outlined in CT images slide by slide and volume of tumor was semi-automatically calculated by computer software (AW 4.6 workstation, GE Healthcare, USA). Percentage of tumor volume change was calculated from difference between initial tumor volume and tumor volume at 3 months after treatment divided by initial tumor volume. Based on tumor response the dogs were classified into four groups using the volumetric criteria. Dogs with complete

disappearance of tumor were classified as complete response, those with tumor volume reducing more than 60% were classified as partial response, and those with tumor volume reducing more than 40% were classified as progressive disease. Dogs which did not meet any criteria were classified as stable disease (Table 1).

Table 1 Volumetric tumor response criteria based on WHO and RECIST guidelines using relationship between area and volumetric change (WHO, 1979; James, 1999; Eisenhauer et al., 2009)

Category	Volumetric criteria
Complete response (CR)	Tumor disappearance
Partial response (PR)	More than 65% reduction in volume
Stable disease (SD)	Tumor volume changes between partial response and progressive disease
Progressive disease (PD)	More than 40% increase in volume

Acute and late radiation side effects were recorded based on the toxicity criteria of Veterinary Radiation Therapy Oncology Group (VRTOG), which classified the severity of toxicity into 3 groups of particular organ such as skin, eye, and mucous membrane (Ladue and Klein, 2001). Progression free interval was calculated from the first day of treatment to the day of local recurrence or distant metastasis presence. Median survival time was calculated from the day of first radiation therapy to the day of death. All dogs were treated with a 6-MV linear accelerator (Clinac 2100CD, Varian Medical Systems, Palo Alto, CA). Three-dimensional computer treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA) was used for individual treatment planning. The dogs were divided into 2 groups based on the intensity of radiation treatment protocol. The definitive radiation protocol applied 18 fractions of 3 Gy to the dogs on a daily basis, whereas the palliative treatment applied 6 fractions of 6 Gy to the dogs on a weekly basis.

Descriptive statistics of the patients such as age, breed, sex and type of tumor were reported. Student *t*-test was used for comparing tumor response in each group. Progression free interval and median survival time were analyzed by Kaplan-Meier; log-rank test was used to assess factors related to treatment outcome. Level of significance was set at $P<0.05$.

Results

In total, 20 dogs were included in this study (Table 2): they were 9 male (45%) and 11 female dogs (55%) with median age of 9.3 years old (range of 5-16 years old) and median body weight of 17.2 kg (range of 4-39 kg). For the breeds of dogs, they were cross-bred (n=6), Poodle (n=3), Cocker Spaniel (n=2), Golden Retriever (n=2), Shih Tzu (n=2), Siberian Husky (n=2), Thai Bangkaew (n=2) and Jack Russel Terrier (n=1). The average duration from presence of clinical signs to beginning of treatment protocol was 42.8 days (range of 7-120 days). The nasal tumors were divided into two groups: the nasal carcinoma group (n=15, 75%), which included nasal adenocarcinoma (n=11, 55%), nasal carcinoma (n=3, 15%) and transitional cell carcinoma (n=1, 5%); and the malignant mesenchymal tumor group (n=5, 25%), which included chondrosarcoma (n=2, 10%), osteosarcoma (n=2, 10%) and fibrosarcoma (n=1, 5%). All dogs in this study were categorized into the $T_3N_0M_0$ group according to the TNM classification system. Twelve dogs (60%) had stage III disease, whereas 8 dogs (40%) had stage IV disease. The median time from presence of clinical signs to beginning of treatment protocol was 30 days (range of 7-120 days).

The mean percentage of tumor volume reduction at 3 months after treatment of dogs in the carcinoma group and malignant mesenchymal tumor group were 49.47% (95%CI 30.07-68.87) and 47.31% (95%CI 35.36-59.26), respectively. Moreover, the mean percentages of tumor volume reduction at 3 months after treatment of the dogs with intranasal tumor in stages III and IV were 45.35% and 54.30%, respectively. No statistical difference in the percentage of tumor volume change before and after radiation was found between these groups (Table 3). Based on the volumetric criteria of tumor measurement, 30% (6/20) of the treated dogs were defined as partial response, while 70% (14/20) of the treated dogs were categorized into stable disease.

At the end of this study (820 days of follow-up time), 11 dogs were still alive, nine dogs had local recurrence and one dog had distant metastasis. The median following time was 278.5 days (range of 116-682 days), median survival time was 383 days (95%CI 214.69-551.31) and median progression free interval was 384 days (95%CI 240.94-527.06).

In this study, factors significantly related to median survival time were the age of dog at the time of treatment and tumor response. More than half of the dogs younger than 8 years old were still alive within 400 days after treatment while those older than 8 years had median survival time of 281 days (95%CI 183.38-378.62) as shown in Fig. 1. The median survival times of dogs in the stable disease and partial response groups were 420 (95%CI not available) and 281 days (95%CI 194.18-367.82), respectively (Fig. 2).

Improvement in clinical signs was found in all 20 dogs (100%). According to VRTOG classification, every dog had skin, oral mucosa and eye radiation side effects; 4 dogs had grade II, patchy moist desquamation without edema of skin, patchy mucositis of oral mucosa and keratoconjunctivitis sicca requiring artificial tear (20%). In addition, 80% (16/20) of the treated dogs had grade I, dry desquamation and alopecia of skin, mild mucositis of oral mucosa and mild conjunctivitis (80%). In addition, late radiation effects and hair color change were found in 4 dogs (20%); retinal degeneration was found in one dog (5%). Stable disease and partial response gave no difference in clinical side effects. Nevertheless, patients in the partial response group showed markedly improved clinical signs after treatment.

Table 2 Topographic details of dogs in the study

Description	n (percentage)
Age (years, range)	9.3 years (5-16 years)
Breed	
Cross-bred	6 (30%)
Poodle	3 (15%)
Golden Retriever	2 (10%)
Shih Tzu	2 (10%)
Siberian Husky	2 (10%)
Thai Bangkeaw	2 (10%)
Jack Russel Terrior	1 (10%)
Sex	
Male	9 (45%)
Female	11 (55%)
Presented signs	
Unilateral epitaxis	9 (45%)
Difficulty in breathing	5 (25%)
Face deformation	4 (20%)
Snoring	4 (20%)
Sneeze	2 (10%)
Nasal discharge	2 (10%)
Histological type	
Carcinoma	15 (75%)
Adenocarcinoma	11 (55%)
Carcinoma	3 (15%)
Transitional cell carcinoma	1 (5%)
Malignant mesenchymal tumor	5 (25%)
Chondrosarcoma	2 (10%)
Osteosarcoma	2 (10%)
Fibrosarcoma	1 (5%)
TNM staging	
T3MoNo	20 (100%)
Modified Adams' CT staging	
T3	12 (60%)
T4	8 (40%)
Radiation protocols	
Definitive protocol	18 (90%)
Palliative protocol	2 (10%)
Radiation side effects	
Acute side effects	
Grade I skin and eye effect	16 (60%)
Grade II skin and eye effect	4 (20%)
Late side effects	
Grade I skin effect	4 (20%)
Grade III eye effect	1 (5%)

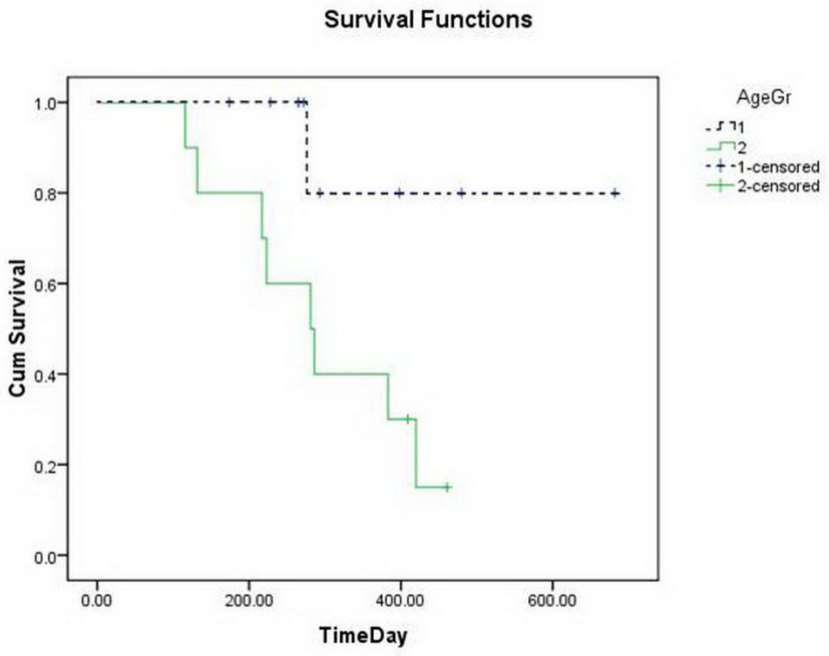

Figure 1 Median survival time of patients in different age groups (group 1: less than 8 years, group 2: more than 8 years)

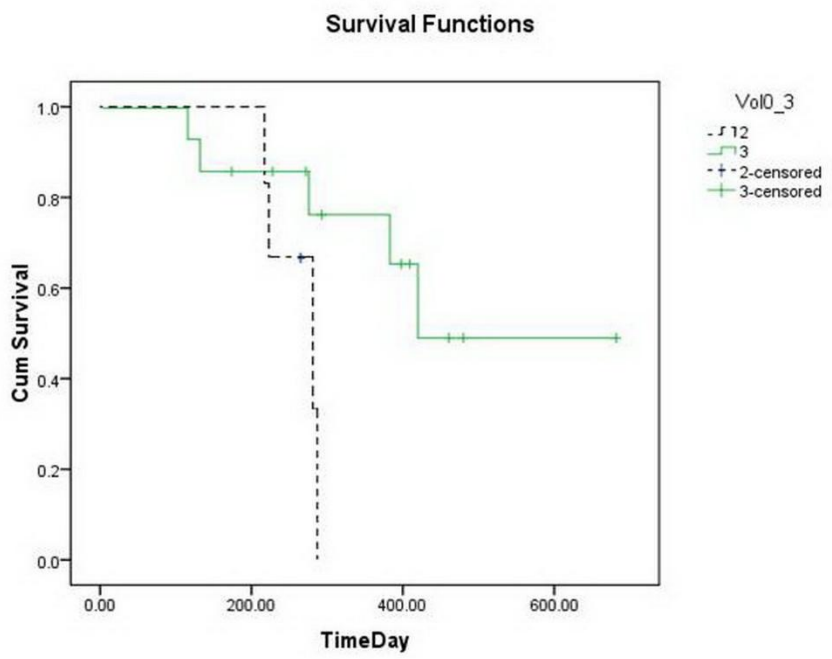

Figure 2 Median survival time of patients in different response groups (group 2: partial response group, group 3: stable disease group)

Table 3 Percentage of tumor volume reduction at three months after radiotherapy and median survival time of dogs in each group

Categories	n	Average percentage of tumor reduction	Median survival time (days)
All dogs	20	48.93% (95%CI 34.70-63.16)	383 (95%CI 214.69-551.31)
Sex			
Male	9	42.21% (95%CI 19.77-64.66)	420 (95%CI 150.16-689.84)
Female	11	54.43% (95%CI 33.17-75.68)	383 (95%CI 180.10-585.90)
Age			
8 years or less	10	48.67% (95%CI 27.64-69.70)	NA[1] (95%CI NA[2])
More than 8 years	10	49.19% (95%CI 25.60-72.79)	281 (95%CI 183.38-378.62)
Tumor Type			
Carcinoma	15	49.47% (95%CI 30.07-68.87)	383 (95%CI 229.21-536.79)
Malignant mesenchymal tumor	5	47.31% (95%CI 35.36-59.26)	NA[1] (95%CI NA[2])
CT stage			
Stage III	12	45.35% (95%CI 27.40-63.29)	420 (95%CI 349.76-490.24)
Stage IV	8	54.30% (95%CI 25.32-83.29)	276 (95%CI 217.45-334.55)
Volumetric response			
PR	6	-	281 (95%CI 194.18-367.82)
SD	14		420 (95%CI NA[2])

NA: not available
[1] Survival curve did not reach 0.5.
[2] 95%CI could not be calculated because survival curve did not reach 0.45.

Discussion

The median survival time for all patients with nasal tumor treated with LINAC in this study was 383 days, which is comparable with that in previous studies. Sones et al. (2013) reported that the median survival time of dogs with intranasal sarcoma was 444 days while Mason et al. (2013) reported that dogs with all types of nasal tumors receiving definitive radiation therapy had a median survival time of 427 days. The longest median survival time in this study was 603 days in the chondrosarcoma patients. Although the survival time of dogs with malignant mesenchymal tumor could not be calculated because more than 50% of the patients were still alive at the end of follow-up time, the dogs in this group tended to have longer survival time than those in the carcinoma group (383 days). This corresponds with the study of Kondo et al. (2008), which reported that the dogs with chondrosarcoma (21.5 months) had longer survival

time than those with adenocarcinoma (2.3 months) treated with radiation therapy.

However, survival time alone is not sufficient for evaluating treatment response; quality of life and efficacy or toxicity of treatment should also be considered. Cancer treatment efficacy is assessed by evaluating changes in tumor burden after treatment. Volumetric measurement is one of the accurate methods for measuring irregular three-dimensional shaped tumors such as intranasal or head and neck tumors because it comes directly from visual tumor burden. This technique could improve the ability to detect both response and progression. Early detection in progressive disease allows patients to stop an ineffective treatment.

The present study demonstrated that the tumor volume in all patients reduced nearly 50% within 3 months after treatment. This contributed to the improved clinical signs in all patients. Generally, tumor shrinkage after treatment should be an indication for better prognosis. However, the correlation between tumor shrinkage and patient survival is still controversial in both human medicine and veterinary field. Based on the results of the present study, the median survival time of the stable disease patients was significantly longer than that of the partial response group although the former had less tumor shrinkage than the latter. The reason of this maybe the variety of tumor growth rate before treatment; a tumor with high growth rate responds well to radiotherapy and if the number of tumor cells remains the same, this cell will divide and grow rapidly after treatment. On the contrary, a tumor with slow growth rate has limited response to radiotherapy and grows slower. From the results, it has been proposed that disease stabilization maybe a better parameter for monitoring tumor response to therapy. Lara et al. (2008) demonstrated that disease control rate was a stronger predictor of survival than objective response rate.

The most common clinical signs of dogs with intranasal tumors are chronic nasal hemorrhage and difficulty in breathing caused by bleeding of nasal tumor as well as obstruction of the nasal passage by a solid tumor in the nasal cavity. The histological type of tumor in this study is similar to several reports in veterinary literatures; 75% was in carcinoma group and 25% was in malignant mesenchymal tumor group (Kondo et al., 2008). However, samples used for diagnosis in case of nasal tumors in KUVTH usually come from rhinoscopy-guided biopsy. This method could take only small pieces of tumor and, as a result, might be difficult for histopathologist to provide a specific final diagnosis of tumor type. Nevertheless, rhinoscopy-guided biopsy is the most less-invasive way to take nasal tissue sample for histopathological diagnosis. All patients in this study were in CT stage III (tumor invading into the peri-orbital area, subcutaneous) and stage IV diseases (tumor invading through cribriform plate), declaring late detection of intranasal tumor. This might demonstrate differences in the attitude of dogs' owners in this area about observing their dogs' common upper respiratory problem.

In summary, radiation therapy is the appropriate treatment for intranasal tumor patients due to extended survival time, manageable complications and increased quality of life. However, the limitation of the present study was the small number of patients contributing to insufficient statistical difference between each group. Nevertheless, this preliminary report will lead to more investigation into the field of volumetric measurement as a prognosis factor of nasal tumor treatment.

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บทคัดย่อ

ผลการรักษามะเร็งโพรงจมูกในสุนัขด้วยรังสีรักษา

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การศึกษานี้มีจุดประสงค์เพื่อประเมินผลการตอบสนองต่อการรักษามะเร็งโพรงจมูกในสุนัขโดยใช้วิธีการวัดปริมาตรของเนื้องอกที่เปลี่ยนแปลงไป สุนัขทั้งหมด 20 ตัวเข้ารับการรักษามะเร็งโพรงจมูกด้วยการฉายรังสีที่โรงพยาบาลสัตว์เพื่อการเรียนการสอน มหาวิทยาลัยเกษตรศาสตร์ ระหว่างเดือนพฤษภาคม พ.ศ. 2556 ถึงเดือนสิงหาคม พ.ศ. 2558 ทำการบันทึกข้อมูลของสัตว์ป่วย ได้แก่ อายุ พันธุ์ เพศ ชนิดของมะเร็ง ระยะของมะเร็ง ชนิดของรังสีที่ได้รับ และผลข้างเคียงจากการฉายรังสี สุนัขทั้งหมดที่เข้าร่วมการศึกษาได้รับการรักษาด้วยการฉายรังสีปริมาณรวม 36-54 Gy และได้รับการตรวจด้วยภาพรังสีส่วนตัดอาศัยคอมพิวเตอร์ก่อนการรักษาและหลังเสร็จสิ้นการรักษา 3 เดือน เพื่อประเมินผลการตอบสนองต่อการรักษาตามหลักของการวัดปริมาตร การศึกษาพบว่าสุนัขทุกตัวมีค่ามัธยฐานระยะเวลารอดชีวิต 383 วัน (95%CI 214.69-551.31) และมีอัตราการรอดชีวิตโดยโรคสงบ (progression free survival; PFS) 384 วัน (95%CI 240.94-527.06) มีสุนัขจัดอยู่ในกลุ่มที่มีการตอบสนองบางส่วนจำนวน 6 ตัว (30%) และอยู่ในกลุ่มที่มีการตอบสนองแบบคงที่จำนวน 14 ตัว (70%) นอกจากนี้ เมื่อศึกษาปัจจัยต่าง ๆ ที่อาจมีผลต่อระยะเวลาการรอดชีวิตโดยใช้ log-rank test พบว่า อายุของสุนัขและการตอบสนองตามหลักการวัดปริมาตรมีผลต่อระยะเวลาการรอดชีวิตอย่างมีนัยสำคัญทางสถิติ ($P<0.05$)

คำสำคัญ: การวัดปริมาตรมะเร็ง มะเร็งโพรงจมูก ระยะเวลาการรอดชีวิต รังสีรักษา

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