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SHORT COMMUNICATION

Clinical Case Report

3D-conformal radiation therapy induced eyelid and corneal acute complications in dogs with head tumors

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Abstract

This study evaluated the incidence of acute eyelid and/or corneal complications (AC) in 172 eyes of 86 dogs with head tumors treated by 3D-conformal radiation therapy (3D-CRT). AC occurred in 24 eyes (13.9%), presenting as blepharoconjunctivitis, non-ulcerative keratitis, ulcerative keratitis, or corneal perforation. Median shortest distance from the ocular center to the tumor margin (DOCT), ocular cumulative exposure dose (OCED), and ocular radiation exposure rate (ORER) in AC cases (12.8 mm, 24.5 Gy, 72.5%) were significantly higher or shorter than in non-AC cases (26.4 mm, 12.6 Gy, 35.0%) ($P < 0.01$). All AC occurred during or within 21 days after 3D-CRT. Receiver operating characteristic curve analysis identified cut-off values for AC prediction: DOCT 17.6 mm, OCED 17.5 Gy, and ORER 55.0%. These parameters may aid in AC risk assessment in canine head tumor radiotherapy.

Key Words: 3D-CRT, cut-off value, eyelid and corneal acute complication

There are three main treatments used alone or in combination for malignant tumors: surgery, chemotherapy, and radiation therapy (RT)^{5,13,15,26–28,30}. Each has advantages and disadvantages^{5,7,13,15,21,26–28,30}. In canine head tumors, complete surgical excision is often difficult because of anatomical limitations and the proximity of critical structures such as the eyes and brain. Therefore, RT plays an important role as a local treatment to achieve tumor control while preserving organ function. In Japan, the use of 3D-conformal radiation therapy (3D-CRT) has recently increased in dogs, particularly for tumors in the head region³⁾. The application of

radiation to tumor tissue can induce tumor cell death or growth inhibition, making RT a viable treatment in areas where surgery is difficult^{1,2,21)}. A high dose of radiation can be delivered to tumor tissues while minimizing exposure to normal tissues; however, depending on tumor location, radiation-associated complications may occur in surrounding normal tissue areas^{9,11,14)}. These complications are classified as either acute or late effects, with some radiation-induced complications healing naturally within a few weeks, such as dermatitis, and others that do not heal, such as cataracts, keratoconjunctivitis sicca, and bone necrosis^{8,10,19,22)}. Complications also occur in the

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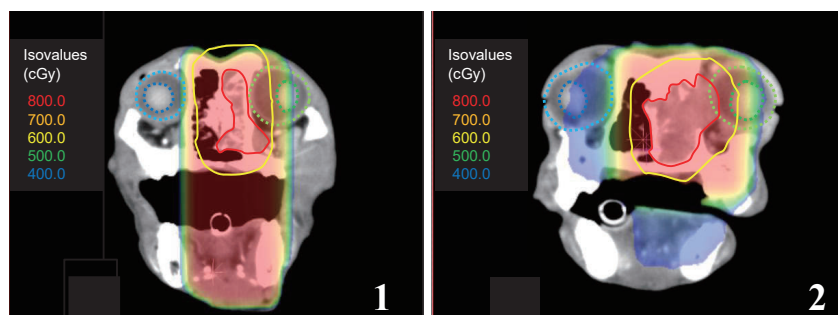


Fig. 1. Representative dose distribution images for nasal cavity tumors treated with 3D-CRT. Images 1 and 2 show the parallel-opposed two-field technique and the four-field technique, respectively. Red labels represent the 100% isodose line, blue labels indicate the 50% isodose line, and yellow contours outline the planning tumor volume (PTV).

eyelid, conjunctiva, and cornea that may affect appearance, cause severe pain, and, in serious cases, lead to vision loss^{8,10,19,22}. However, data are limited worldwide, and particularly scarce in Japan, on canine eyelid and corneal acute ocular complications induced by both 3D-CRT with old type of RT devices and advanced one including intensity-modulated RT (IMRT). To address this, we retrospectively examined the incidence of eyelid and corneal acute complications (AC) in dogs with head tumors treated using 3D-CRT, and relationships among 3D-CRT conditions and the incidence of these AC.

Between October 2019 and December 2020, 172 eyes of 86 dogs with head tumors that underwent 3D-CRT by using a linear accelerator with an X-ray energy output of 4 MV (Primus Mid Energy; Canon Medical Systems, Tochigi, Japan) at the Osaka Prefecture University Veterinary Medical Center (OPUVMC) were extracted from the electronic medical records. For RT, planning CT scans were obtained for each dog in the treatment position using a bite block and vacuum-mattress immobilization device. Treatment plans were created with a 3D CT-based planning system (Xio; Elekta Japan, Tokyo). The gross tumor volume (GTV) was defined as the contrast-enhancing area on CT. A clinical target volume (CTV) was delineated by extending 0.3–0.8 cm beyond the GTV to encompass potential microscopic disease. A 0.2 cm margin was then added in all directions to define the planning target volume (PTV). Beam arrangements and

isocenter were determined based on tumor location and adjacent critical structures. Beam arrangements were determined with the primary aim of minimizing radiation exposure to normal tissues adjacent to the tumor. Radiation was delivered using parallel-opposed or four-field techniques with 4 MV X-rays, and representative dose distribution images are shown (Fig. 1). Dose and fractionation schedules were individualized. Portal imaging was performed before the initial session to confirm patient positioning.

Radiation-induced complications were defined as those in which no pre-existing ocular disorders were observed before 3D-CRT, with complications detected following 3D-CRT commencement. The diagnosis of AC was made by the veterinary radiation therapist, a certified radiological protection supervisor, and/or the veterinary ophthalmology specialist. In the former, diagnoses reflected clinical symptoms observed during visual inspection, while in the latter, general ophthalmic examination including visual inspection, Schirmer tear test (STT, Ayumi Pharmaceutical, Tokyo, Japan), slit-lamp examination (portable slit lamp SL-15, Kowa, Aichi, Japan) containing vital dye staining (Flores Eye Test Strips 0.7 mg, No. 87729, Ayumi Pharmaceutical, Tokyo, Japan), assessment of intraocular pressure (TV01, Icare, Vantaa, Finland), and posterior segment ophthalmoscopy examination were performed. AC were classified into four categories; 1) Blepharoconjunctivitis, defined by ocular discharge, blepharospasm, hyperemia, edema, or thickening of the eyelid and



Fig. 2. Typical ocular appearance of acute complications associated with 3D-CRT. Photos 1, 2, 3, and 4 show blepharoconjunctivitis, non-ulcerative keratitis, ulcerative keratitis, and corneal perforation, respectively.

conjunctiva, alopecia and/or concurrent keratitis, 2) Non-ulcerative keratitis, defined by decreased clarity of the cornea, corneal edema, inflammatory cell infiltration, neovascularization, and/or ocular discharge, 3) Ulcerative keratitis, defined by corneal inflammation with loss of the corneal epithelium or variable amount of the corneal stroma, and 4) Corneal perforation, with various conditions of keratitis. Acute complications were defined as those occurring within 90 days after the completion of treatment, based on the general criteria of the Veterinary Radiation Therapy Oncology Group (VROG)^{14,23}.

Cases treated with 3D-CRT were evaluated for breed, age, sex, tumor type, tumor location, targeted tumor radiation dose, ocular cumulative exposure dose (OCED), and ocular radiation exposure rate (ORER). The targeted tumor radiation dose was calculated by determining the dose per radiation session for the targeted tumor, then multiplying by the number of sessions to obtain the total targeted tumor radiation dose. The shortest distance from the ocular center to the tumor margin (DOCT) was measured using three-dimensional reconstructed CT images. Regarding the targeted tumor radiation dose and the ocular exposure dose (OED), the radiation dose per session for the targeted tumor and the

eye exposure dose per session were estimated from the radiation treatment plan. These values were multiplied by the number of sessions to calculate total targeted tumor dose and total OED. OCED was calculated by multiplying the average ocular exposure dose per session by the number of 3D-CRT sessions. ORER was obtained for each eye by the formula: $[\text{OCED} \times 100 / \text{targeted tumor radiation dose}]$ and expressed as exposure percentage. The presence or absence of eye protection during RT in AC cases were also assessed. Then, cutoff values for DOCT, OCED, and ORER that potentially contribute to AC were calculated.

Results are expressed as medians (first quartile to third quartile). To compare DOCT, OCED, and ORER between eyes with and without AC, a parametric Welch's t-test was performed for statistical significance with a P -value < 0.01 considered statistically significant. Also, to determine cutoff values for DOCT, OCED, and ORER, receiver operating characteristic (ROC) curve analysis was conducted, with respective cutoff values, sensitivity, and specificity calculated.

The acute complications associated with 3D-CRT were observed in 24 eyes of 14 dogs (Table 1) among 172 eyes of 86 dogs with head tumors (Supplemental Tables 1-3), accounting for an incidence of 13.9%. The symptom breakdown for the 24 eyes with AC is as follows: blepharoconjunctivitis in 7 eyes of 4 cases, non-ulcerative keratitis in 16 eyes of 9 cases, ulcerative keratitis in 6 eyes of 4 cases, and corneal perforation in one eye of 1 case (Table 1, Fig. 2). The onset of AC occurred during 3D-CRT in 16 eyes and within three weeks post-RT in 8 eyes, indicating that all cases developed in the acute phase. Regarding the primary tumor site, nasal and intranasal tumors were most common, observed in 14 eyes of 7 cases (58.3%), followed by lip and oral cavity tumors in 8 eyes of 6 cases (33.3%) and intracranial tumors in 2 eyes of 1 case (8.3%) (Table 1). Additionally, AC developed bilaterally in 20 eyes of 10 cases and unilaterally in 4 eyes of 4 cases (Table 1). All ocular disorders except corneal perforation improved with medical treatments. For the 1 eye with corneal perforation,

Table 1. Overview of acute complications cases in 24 eyes of 14 dogs associated with 3D-CRT

Case number	Breed Age (years old) / Sex	Affected tumor (Tumor location)	Target tumor radiation dose (Gy) (Dose × numbers of irradiations / Irradiations per week)	Side	Ocular cumulative exposure dose (Gy)	Ocular radiation exposure rate (%)	Complications	Days of complication onset after first irradiation
P1	Labrador Retriever 11 / Female	Mast cell tumor (Both side of Nasal bridge)	45 (3 × 15 / 3)	OD	25.2	56.0	Non-ulcerative keratitis	39 (4 days after RT)
				OS	28.1	62.3	Non-ulcerative keratitis	39 (4 days after RT)
P2	Toy Poodle 13 / Male	Adenocarcinoma (Right nasal cavity)	40 (4 × 10 / 3)	OD	28.8	72.0	Blepharoconjunctivitis Non-ulcerative keratitis	42 (20 days after RT)
				OS	25	62.5	Blepharoconjunctivitis Non-ulcerative keratitis	42 (20 days after RT)
P3	Toy Poodle 14 / Female	Meningioma (intracranial)	36 (3 × 12 / 3)	OD	27.6	76.7	Blepharoconjunctivitis Non-ulcerative keratitis	28 (Under RT)
				OS	24.8	69.0	Blepharoconjunctivitis	28 (Under RT)
P4	Toy Poodle 14 / Male	Melanoma (Right maxilla)	32 (8 × 4 / 1)	OD	22.4	69.9	Non-ulcerative keratitis	21 (Under RT)
				OS	18.5	57.9	None	. . .
P5	Toy Poodle 12 / Female	Squamous cell carcinoma (Both side of labial region)	32 (8 × 4 / 1)	OD	23.8	74.4	Non-ulcerative keratitis	21 (Under RT)
				OS	24.1	75.4	Ulcerative keratitis	21 (Under RT)
P6	Toy Poodle 11 / Male	Melanoma (Left maxilla)	32 (8 × 4 / 1)	OD	22.6	70.5	Non-ulcerative keratitis	21 (Under RT)
				OS	26.7	83.4	Non-ulcerative keratitis	21 (Under RT)
P7	Toy Poodle 10 / Male	Undifferentiated carcinoma (Left nasal cavity)	32 (8 × 4 / 1)	OD	17.5	54.8	Blepharoconjunctivitis	21 (Under RT)
				OS	23.5	73.5	Blepharoconjunctivitis Non-ulcerative keratitis	21 (Under RT)
P8	Miniature Dachshund 16 / Male	Adenocarcinoma (Both side of nasal cavity)	32 (8 × 4 / 1)	OD	25.1	78.5	Non-ulcerative keratitis	35 (7 days after RT)
				OS	25.8	80.5	Blepharoconjunctivitis Non-ulcerative keratitis	35 (7 days after RT)
P9	Pekingese 15 / Male	Melanoma (Right maxilla)	32 (8 × 4 / 1)	OD	25.4	79.4	Ulcerative keratitis	21 (Under RT)
				OS	15.5	48.4	None	. . .
P10	Mixed breed 15 / Male	Adenocarcinoma (Left nasal cavity)	32 (8 × 4 / 1)	OD	23.7	74.0	Ulcerative keratitis	21 (Under RT)
				OS	16.1	50.4	Non-ulcerative keratitis	21 (Under RT)
P11	West Highland White Terrier 14 / Male	Adenocarcinoma (Left frontal sinus)	32 (8 × 4 / 1)	OD	18.3	57.1	Non-ulcerative keratitis	49 (21 days after RT)
				OS	27.9	87.3	Ulcerative keratitis	49 (21 days after RT)
P12	Standard Poodle 14 / Male	Melanoma (Left maxilla)	32 (8 × 4 / 1)	OD	8.3	26.0	None	. . .
				OS	22.1	69.1	Ulcerative keratitis	21 (Under RT)
P13	Yorkshire Terrier 12 / Male	Adenocarcinoma (Right nasal cavity)	32 (8 × 4 / 1)	OD	23.3	72.8	Non-ulcerative keratitis	21 (Under RT)
				OS	25.1	78.4	Non-ulcerative keratitis	21 (Under RT)
P14	Cocker Spaniel 10 / Female	Apocrine gland carcinoma (Right maxilla)	32 (8 × 4 / 1)	OD	22.4	69.9	Corneal perforation	21 (Under RT)
				OS	8.8	27.6	None	. . .

3D-CRT: 3D-conformal radiation therapy, OD: right eye, OS: left eye, RT: radiation therapy

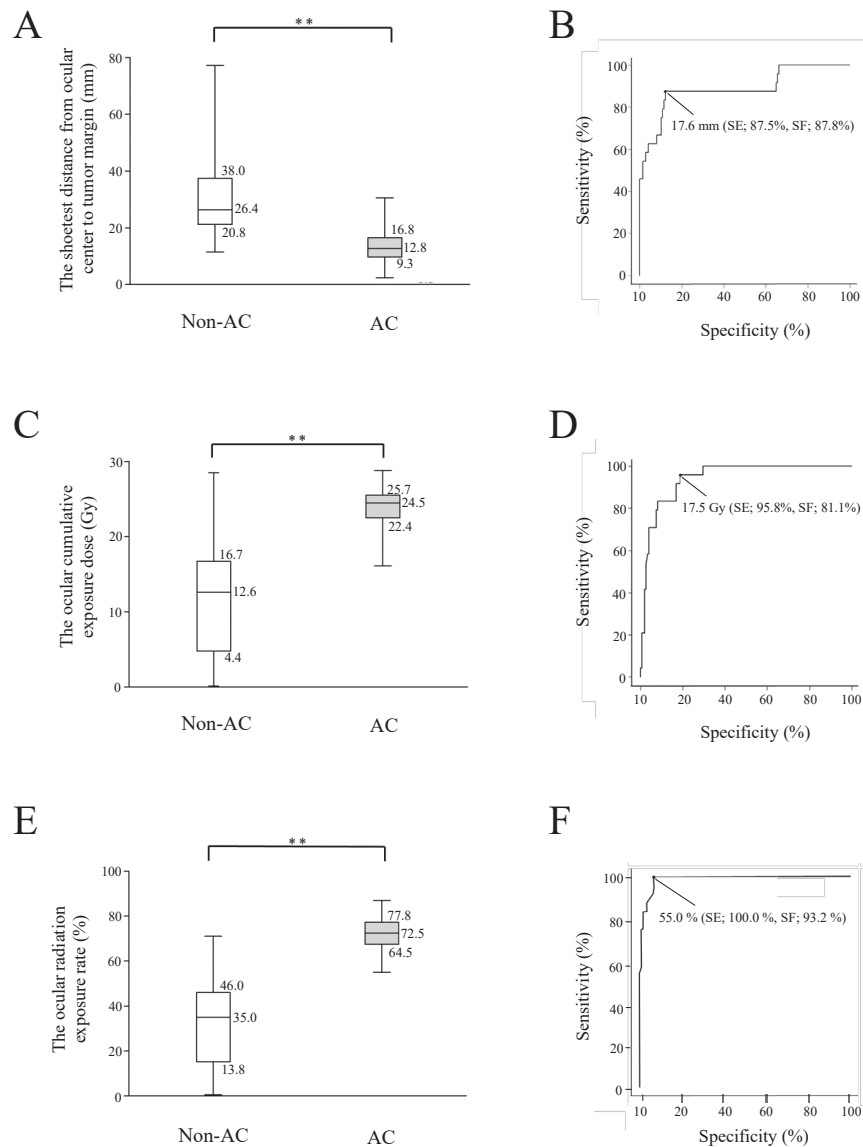


Fig. 3. Comparison of ocular radiation parameters by receiver operating characteristic (ROC) curve analysis between acute complications (AC) and non-AC cases.

A; The shortest distance from ocular center to the tumor margin (DOCT), B; ROC curve analysis for DOCT with the cut-off value, C; The ocular cumulative exposure dose (OCED), D; ROC curve analysis for OCED with the cut-off value, E; The ocular radiation exposure rate (ORER), F; ROC curve analysis for ORER with the cut-off value. In the box plots, the upper and lower hinges represent the third and first quartiles, respectively. The line within the box indicates the median, and whiskers denote the maximum and minimum values. Double asterisks indicate a significant difference at $P < 0.01$. The numbers in the ROC curves represent the cut-off values (SE; sensitivity, SF; specificity).

medical treatments were unsuccessful, although prognosis after enucleation was good. No secondary infections were observed in any of the cases. In addition, statistical analysis revealed no significant associations between the incidence of acute complications and clinical factors, including breed, tumor type, tumor location, or irradiation method.

For all 172 eyes of 86 dogs that underwent 3D-CRT, no ocular protection was implemented during treatment. The median DOCT in non-AC cases was 26.4 mm (20.8–38.0 mm), whereas in AC cases, it was 12.8 mm (9.3–16.8 mm) (Fig. 3A). In the eyes of non-AC cases, the median OCED and its ORER were 12.6 Gy (4.4–16.7 Gy) and 35.0% (13.8%–46.0%), respectively (Figs. 3C &

3E), whereas in the eyes of AC cases, OCED and ORER values were significantly higher at 24.5 Gy (22.4–25.7 Gy) and 72.5% (64.5%–77.8%), respectively (Figs. 3C & 3E, $P < 0.01$). The cut-off value for DOCT was 17.6 mm, with a sensitivity of 87.5%, specificity of 87.8%, an area under the ROC curve (AUC) of 0.89, and a 95% confidence interval (CI) of 0.80–0.98 (Fig. 3B). The cut-off value for OCED was 17.5 Gy, with a sensitivity of 95.8%, specificity of 81.1%, an AUC of 0.94, and a 95% CI of 0.90–0.99 (Fig. 3D). The cut-off value for ORER was 55.0%, with a sensitivity of 100%, specificity of 93.2%, an AUC of 0.99, and a 95% CI of 0.98–1.00 (Fig. 3F).

For treatments conducted at the OPUVMC, when tumors were located near the eye, ACs associated with 3D-CRT were observed (Fig. 3A). This is natural given the lack of ocular protection used during 3D-CRT. With increased radiation exposure comes an increased likelihood of radiation damage⁴. Also, the highest radiation dosage for the targeted tumor is often used, with damage to peripheral tissues reflecting attenuation due to distance from the targeted tumor¹⁶.

In this study, ACs were observed with a certain frequency in dogs treated with a 3D-CRT device. These complications, which are now considered uncommon due to advances in radiation delivery techniques such as IMRT and the use of appropriate shielding^{12,31}, reflect clinical challenges associated with earlier-generation equipment. With this 3D-CRT machine, it was difficult to completely prevent ocular complications through treatment planning. Our findings highlight the importance of proper planning and shielding, even with older machines, and provide retrospective insight into the limitations of 3D-CRT that was in use at our institution.

Blepharoconjunctivitis associated with 3D-CRT occurred at an incidence rate of 54.8% to 80.5% for ocular exposure (Table 1). This condition involves dermatitis around the eye, triggered by radiation-induced hypoplasia of the basal epithelial stem cell layer²⁴. The Zeiss glands, which secrete lipids to the eyelids, and meibomian glands, which secrete lipids to the cornea, are

highly radiation-sensitive²⁵. Damage to these glands exacerbates inflammation involving the eyelid, conjunctiva, and cornea²⁵. Non-ulcerative keratitis associated with 3D-CRT was induced at an ocular exposure rate of 56.0% to 83.4%, while ulcerative keratitis occurred at a rate of 69.1% to 87.3% (Table 1). Causes may include²⁵ direct damage to the corneal surface epithelium by 3D-CRT, possibly damaging deeper layers of the corneal epithelium and stroma. Radiation is also thought to induce corneal epithelial and stromal cell hypoplasia²⁴. This may result from secondary tear film deficiencies caused by dry eye syndrome (keratoconjunctivitis sicca), which arises from the loss of the tear film^{6,24,25}. Reduced tear production or increased tear evaporation due to radiation exposure are major causes of insufficient tears on the ocular surface^{24,25}. Corneal perforation associated with 3D-CRT occurred at an ocular exposure rate of 69.9% (Table 1). Causes may include hypoplasia of corneal epithelial and stromal cells, tear layer deficiencies, and trauma from mechanical stress and secondary infections due to the loss of epithelial barrier function, exacerbating side effects⁶.

The bismuth-coated latex shield (hereafter referred to as B-shield), used for human patients, reduces average radiation dose to the eye by approximately 60%¹⁸. However, this method is not established for veterinary medicine. One reason for this may be that such shielding can lead to scattered radiation due to the barriers, potentially preventing sufficient radiation dosage to the targeted tumor. For human patients in which the B-shield is difficult to apply, an increase in radiation attenuation is suggested to occur with higher moisture content in the shield¹⁷. Therefore, either a combination of viscoelastic hydroxyethyl cellulose ophthalmic solutions with soft contact lenses, or partial eyelid suturing with the introduction of viscoelastic substances underneath, may provide protection. Given that radiation damage to the cornea is likely caused by the lack of tear film on the corneal epithelium^{6,22,24,25}, these aqueous preparations may be the most effective protective method currently available. Additionally, applying

autologous serum, hyaluronic acid preparations, and/or ophthalmic ointments to the eye and eyelid area may help protect the skin, Zeiss glands, and meibomian glands, potentially reducing the extent of radiation damage²²⁾.

In this study, both once- and thrice-weekly fractionation schedules were analyzed together, as the fractionation frequency itself was not considered a major determinant of acute ocular complications. This is because such complications are more likely associated with the total dose and the proximity of the eye to the irradiated target, rather than the treatment interval. However, further investigation considering the influence of fractionation frequency may provide additional insights in future studies.

In cases that fall outside the cut-off values, the risk of developing AC is considered high. Therefore, it may be effective to immediately implement preventive measures after radiation exposure, such as applying hyaluronic acid preparations to protect the cornea, or ointments, such as non-steroidal anti-inflammatory drugs and/or very low concentrations of steroids, to the eyelid area. Frequent ophthalmic examinations by veterinary ophthalmologists are necessary for early-stage ocular abnormality identification. It is also important to selectively apply radiation to the targeted tumor and reduce radiation dose to the eyelid and cornea.

For the assessment of acute ocular complications, four ophthalmology-based categories were applied. Although standardized criteria such as the VRTOG grading system should ideally be used for toxicity assessment, we focused on the localized ophthalmic region and therefore adopted specific categories that could better capture periocular and corneal lesions. As this retrospective evaluation revealed significant clinical findings, future prospective studies incorporating both ophthalmic grading and standardized toxicity criteria such as VRTOG are expected to provide more comprehensive insights.

Recent advances in radiotherapy techniques, such as volumetric modulated arc radiation therapy²⁰⁾ and other IMRT²⁹⁾ methods, have enabled more precise dose delivery and improved

sparing of normal tissues. Considering the present findings, future studies employing these techniques may further enhance dose conformity to the target while reducing radiation exposure to periocular structures, potentially decreasing the incidence of ocular complications. Because physical shielding is often difficult to apply in veterinary patients, these advanced dose-modulation techniques may represent the most practical approach to improving treatment safety in the future.

Late-onset radiation-induced ocular complications, including corneal scarring, keratoconjunctivitis sicca, cataract, and retinopathy, may occur in a dose-dependent manner²²⁾. Long-term follow-up and further investigation focusing on dose optimization will be important to reduce the risk of such late toxicities.

In this study, bolus application was used in some cases during radiotherapy. Although bolus use may be associated with the occurrence of acute ocular complications, the number of applicable cases was limited in the present study, and no statistically significant relationship was identified. Further prospective studies that incorporate bolus usage as an evaluation factor will be required to clarify its potential impact.

One study limitation is that this is a retrospective study, and detailed ophthalmic examinations were not performed under the supervision of a veterinary ophthalmologist for all dogs in the study. Therefore, mild or subclinical ocular changes might have been overlooked, which could have influenced the calculated incidence of acute complications. To improve the diagnostic accuracy for ocular abnormalities, a significant side effect associated with 3D-CRT, collaboration with veterinary ophthalmologists is essential to enhance diagnosis and establish appropriate treatment protocols. Also, as the number of cases is insufficient, further evaluation is necessary to accurately estimate and validate appropriate cut-off values.

In conclusion, AC associated with RT occurred at a certain level when 3D-CRT was applied to canine head tumors. To prevent the occurrence of AC, it is advisable to maintain cumulative

radiation dose to the eye below 17.5 Gy and ORER below 55.0% during treatment. Ocular protection during 3D-CRT is also important, along with appropriate treatments guided by frequent ophthalmic examination, when a high incidence of AC is anticipated.

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Conflict of interest

The authors declare no conflict of interest.

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