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Original Article

Dosimetric parameters predictive of nasolacrimal duct obstruction after carbon-ion radiotherapy for head and neck carcinoma

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ABSTRACT

Background and purpose: Little information is available on the risk factors for nasolacrimal duct obstruction after radiotherapy for head and neck tumors. We investigated the incidence and predictive dosimetric parameters for nasolacrimal duct obstruction following carbon-ion radiotherapy for head and neck tumors.

Materials and methods: Twenty-eight patients with head and neck non-squamous cell carcinoma were analyzed in this single-institution prospective study. More than half of the tumors were located in the nasal cavity and maxillary sinus. Carbon-ion radiotherapy consisting of 57.6 or 64.0 Gy(relative biological effectiveness; RBE) in 16 fractions was administered. Nasolacrimal duct obstruction was recorded according to Common Terminology Criteria for Adverse Events version 4.0. Cutoff values were determined using receiver operating characteristic (ROC) curve analysis. VX indicates the volume irradiated with X Gy (RBE).

Results: The median follow-up period was 60.3 months. Incidences of Grade 1 and 2 nasolacrimal duct obstructions were 46% (13/28) and 7% (2/28), respectively; no Grade 3 or greater toxicities were recorded. Throughout the dose range, the volumes of the irradiated nasolacrimal ducts were significantly higher in the obstruction-positive patients than in the obstruction-negative patients ($p < 0.001$ for V10, V20, V30, V40, V50, and V60). Cutoff values determined by the ROC curve analysis classified the obstruction-positive patients with an accuracy of >96% over the entire range of V10–V60.

Conclusion: The incidence and predictive dosimetric parameters for nasolacrimal duct obstruction after carbon-ion radiotherapy were demonstrated in a prospective cohort. These data should help optimize carbon-ion radiotherapy treatments for patients with head and neck tumors.

Non-squamous cell carcinoma (NSCC) in the head and neck region is resistant to photon therapy and chemotherapy, and therefore the standard therapy for this disease remains a subject of debate. Previous studies indicated that carbon-ion radiotherapy provides favorable local control and survival for head and neck NSCCs [1–4]. Differing from squamous cell carcinomas of the head and neck region, which are predominantly located in the oral cavity and pharynx, more than 50% of NSCCs arising in the head and neck region are located in the sinonasal cavity [5]. Therefore, the organs at risk (OARs) in radiotherapy for head and neck NSCCs include the maxilla, optical pathway, brain stem, and nasolacrimal duct. The adverse effects related to these OARs include maxillary osteoradionecrosis, visual loss, brain necrosis, and nasolacrimal duct obstruction. Several studies have reported the incidence of maxillary osteoradionecrosis, visual loss, and brain necrosis after carbon-ion radiotherapy, as well as the prediction of risks according to the dosimetric parameters [6–10]; however, the risks for nasolacrimal duct obstruction have not been fully elucidated.

The major symptom of nasolacrimal duct obstruction is watering eyes (epiphora). Although a watering eye does not affect survival, it does affect the quality of life (QOL) of the patient, which is an issue of high importance, because carbon-ion radiotherapy can provide long-term survival [5]. Importantly, carbon-ion radiotherapy is more capable of sparing normal tissues than photon

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therapy [11]. Therefore, identification of the dosimetric parameters predictive of the risk of nasolacrimal duct obstruction will contribute to optimizing treatment planning, and may lead to improved QOL for patients with head and neck tumors treated with carbon-ion radiotherapy. We therefore investigated the incidence of nasolacrimal duct obstruction in a prospective cohort of patients with head and neck NSCC treated by carbon-ion radiotherapy, and performed a dose–volume analysis for this adverse effect.

Materials and methods

Patient characteristics

Patients with head and neck NSCC and who were prescribed carbon-ion radiotherapy at Gunma University Heavy Ion Medical Center were enrolled in this prospective study. Details of the study design and inclusion criteria are described in a previous report [5]. Of the 35 patients registered in the prospective study, seven patients were excluded from this analysis: six patients whose follow-up period was less than 24 months and one patient who received salvage re-irradiation for local recurrence. The characteristics of the 28 patients analyzed in the present study are summarized in Table 1. This study was approved by the institutional review board of Gunma University Hospital and registered with the University Hospital Medical Information Network in Japan (trial registration number: UMIN000007886).

Carbon-ion radiotherapy planning and treatment

In clinical practice, the prescribed dose of carbon-ion radiotherapy is described using the unit Gy(RBE), which is defined as the physical dose (Gy) multiplied by the RBE value of the carbon ions, with RBE being the relative biological effectiveness. The biological NIRS-model, based on the linear-quadratic (LQ) model, was used for calculating the biological dose [12]. Details of the carbon-ion radiotherapy planning and treatment are described in a previous report [5]. Briefly, patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) and immobilized using thermoplastic shells (Shellfitter; Kuraray, Osaka, Japan), with a mouthpiece being created to maintain the position of the lower jaw. Computed tomography (CT) images were acquired at 2 mm slice thickness and used for the treatment planning. The voxel dimensions of all CT images were approximately $0.88 \times 0.88 \times 2.0$ mm. Contrast-enhanced magnetic resonance imaging (MRI) was also performed to assist in target delineation. Two clinical target volumes CTV1 and CTV2 were delineated, with CTV1 encompassing the whole anatomical site of the tumor origin (e.g., nasal cavity or maxillary sinus), and CTV2 being based on the tumor. Two planning target volumes PTV1 and PTV2 were also created, with these having 2 mm margins around CTV1 and CTV2, respectively. In principle, 64.0 Gy (RBE) in 16 fractions was delivered to the patients, with 57.6 Gy (RBE) in 16 fractions being selected in cases where the tumor was adjacent to skin or mucosa. In all cases, the PTV1 was irradiated with 36 Gy(RBE), and the PTV2 was irradiated with the remaining dose.

Assessment of nasolacrimal duct obstruction

Patients received follow-up consultations every month for the first 6 months, and then every 3 months thereafter. MRI and CT were carried out alternately every 3 months, and 18-fluorodeoxyglucose positron emission tomography was carried out every year. Nasolacrimal duct obstruction was evaluated according to the symptom of watering eyes on the basis of the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0), where Grades 1, 2, and 3 are defined as "intervention not indicated", "intervention indicated", and "operative intervention indicated", respectively (N.B., watering eye Grades 4 and 5 are not defined in CTCAEv4.0). The maximum grade recorded during the follow-up period was used for the analysis. The follow-up period was calculated from the first day of irradiation.

Table 1
Patient characteristics.

	All (n = 28)	Nasolacrimal duct obstruction	
		Positive (n = 15)	Negative (n = 13)
Age			
Median (range)	59 (31–77)	60 (31–77)	52 (32–74)
Gender			
Male	13	8	5
Female	15	7	8
Performance status			
0	11	6	5
1	17	9	8
Histology			
Adenoid cystic carcinoma	17	9	7
Olfactory neuroblastoma	5	5	0
Mucoepidermoid carcinoma	2	0	2
Adenocarcinoma	1	0	1
Others*	3	1	2
Primary tumor site			
Nasal cavity	9	8	1
Maxillary sinus	6	6	0
Parotid gland	5	0	5
Pharynx	4	1	3
Oral cavity	3	0	3
External auditory canal	1	0	1
Operability			
Operable	12	6	6
Inoperable	16	9	7
Primary or recurrence			
Primary tumor	25	14	11
Postoperative recurrence			
T stage			
T2	5	2	3
T3	7	4	3
T4	16	9	7
N stage			
N0	28	15	13
Carbon-ion dose			
64.0 Gy(RBE)/16 fractions	25	14	11
57.6 Gy(RBE)/16 fractions	3	1	2
Diabetes mellitus			
Yes	3	1	2
No	25	14	11
Nasolacrimal duct invasion			
Yes	8	8	0
No	20	7	13

* Basal cell adenocarcinoma (n = 1), mucinous carcinoma (n = 1), and carcinoma ex pleomorphic adenoma (n = 1). RBE, relative biological effectiveness.

Dose–volume analysis of the nasolacrimal duct

The nasolacrimal ducts on the same patient side as the tumor were delineated following the definition by Maliborski et al. [13], i.e., the interosseous portion of the nasolacrimal ducts and lacrimal sac (Fig. 1). Dose–volume analysis of the nasolacrimal ducts was performed using MIM Maestro (version 6.8.7.; MIM Software, Inc., Cleveland, OH, USA), with VX indicating the volume of the nasolacrimal duct irradiated with X Gy(RBE).

Statistical analysis

The cumulative incidence of nasolacrimal duct obstruction was evaluated using the Kaplan–Meier method, and the differences

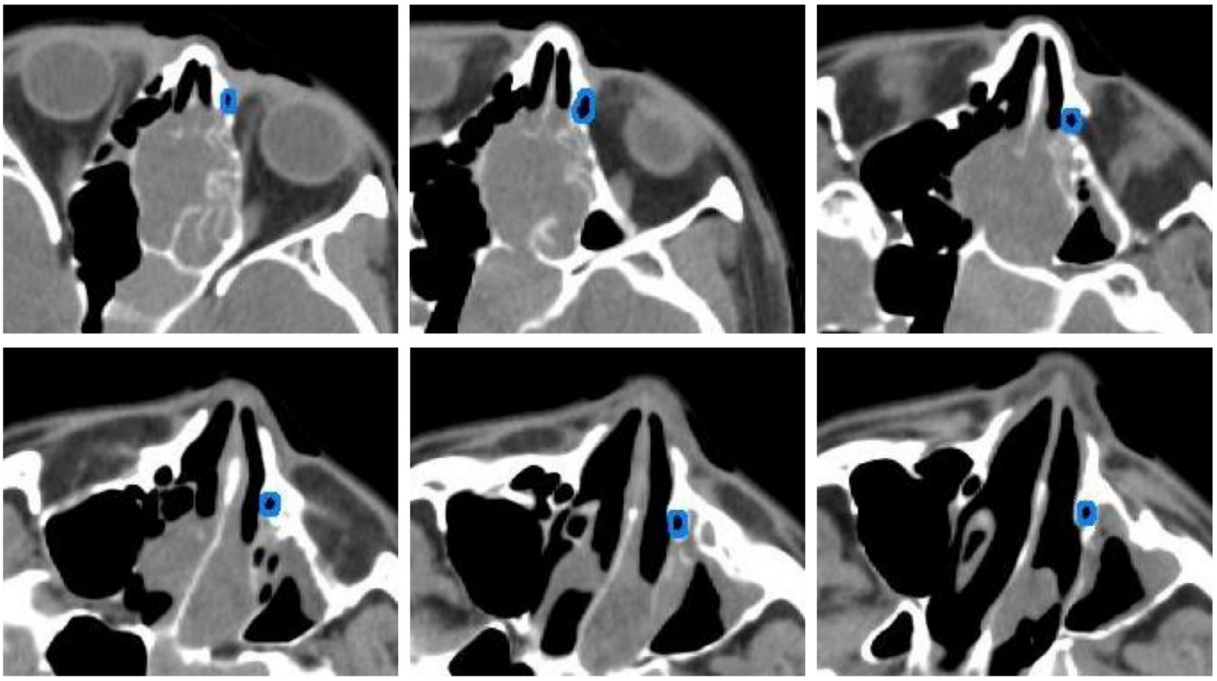

Fig. 1. Representative computed tomography images used for delineation of the nasolacrimal duct. The nasolacrimal duct is indicated in blue.

between two groups were assessed with a log-rank test. The presence of patient-related predictive factors for nasolacrimal obstruction was examined by univariate analysis using the Cox proportional hazards model. Multivariate analysis was not performed, to avoid overfitting due to the small number of events. Cutoff values for VX for classifying nasolacrimal duct obstruction were determined using receiver operating characteristic (ROC) curve analysis. Differences in the values between two groups were examined using the Mann–Whitney test. A p-value below 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 25; SPSS Inc., Chicago, IL, USA).

Results

We first investigated the incidence of nasolacrimal duct obstruction after carbon-ion radiotherapy. The median follow-up period was 60.3 months (range, 24.2–87.0 months), and Grade 1 and 2 nasolacrimal duct obstructions were observed in 46% (13/28) and 7% (2/28) of patients, respectively. No Grade of 3 or greater was recorded. The median interval from initiation of carbon-ion radiotherapy to occurrence of nasolacrimal duct obstruction was 5.0 months (range, 0.7–43.7 months), with 73% (11/15) of nasolacrimal duct obstructions occurring within 1 year of the initiation of carbon-ion radiotherapy. The 5 year cumulative incidence of a Grade 1 or greater nasolacrimal duct obstruction was 54.1% (Fig. 2). Two patients who experienced Grade 2 nasolacrimal duct obstruction underwent dacryocystorhinostomy (i.e., silicone nasolacrimal intubation) at 12 and 42 months after carbon-ion radiotherapy; the former patient had a recurrence of watering eye after the dacryocystorhinostomy, which was salvaged by re-intervention.

To identify the dosimetric parameters associated with nasolacrimal duct obstruction after carbon-ion radiotherapy, we next performed dose–volume analysis for the nasolacrimal ducts. The volumes of the nasolacrimal ducts irradiated with carbon ions were significantly higher in those patients who experienced nasolacrimal duct obstruction than in those who did not, with this being the case throughout the dose range ($p < 0.001$ for all doses

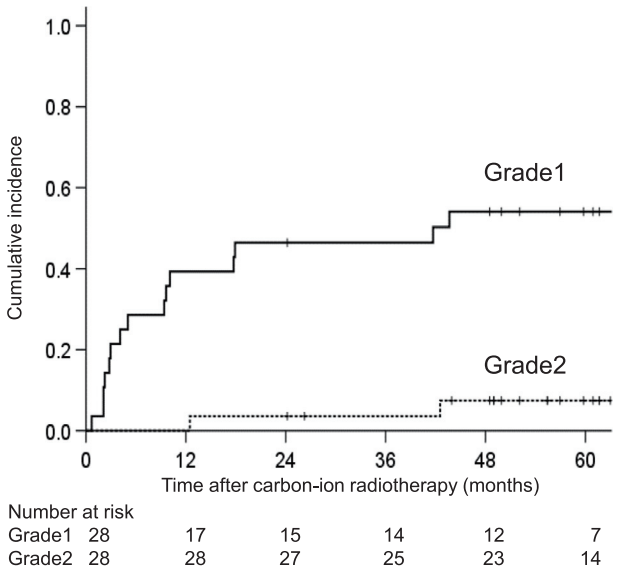

Fig. 2. Cumulative incidence of Grade 1 or Grade 2 nasolacrimal duct obstruction after carbon-ion radiotherapy in patients with head and neck non-squamous cell carcinoma ($n = 28$).

of V10, V20, V30, V40, V50, and V60; Fig. 3). Accordingly, the maximum dose delivered to the nasolacrimal ducts in the obstruction-positive patients was significantly higher than in the obstruction-negative patients (64.6 ± 4.1 Gy(RBE) vs. 2.6 ± 23.4 Gy(RBE), $p < 0.001$). The mean dose delivered to the nasolacrimal ducts in the obstruction-positive patients was also significantly higher than in the obstruction-negative patients (60.7 ± 9.6 Gy(RBE) vs. 0.3 ± 12.9 Gy(RBE), $p < 0.001$). Of note, there was no significant difference in the volume of the delineated nasolacrimal ducts between the obstruction-positive and obstruction-negative patients (0.42 ± 0.14 ml vs. 0.33 ± 0.19 ml, $p = 0.098$).

Having clearly shown the contribution of carbon-ion irradiation to the development of nasolacrimal duct obstruction, we then

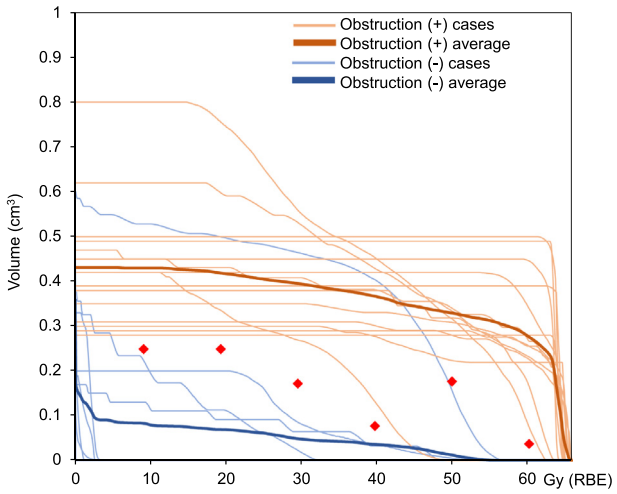

Fig. 3. Cumulative dose–volume histograms for the nasolacrimal ducts in patients with head and neck non-squamous cell carcinoma treated with carbon-ion radiotherapy. Orange and blue lines indicate the obstruction-positive (n = 15) and obstruction-negative (n = 13) patients, respectively. Bold lines indicate the average for each group. Diamonds show the cutoff values at every 10 Gy(RBE) calculated by receiver operating characteristic analysis.

sought to determine the dosimetric parameters predictive of this adverse effect. To this end, we performed ROC curve analysis using the dose–volume data for the nasolacrimal ducts. The resulting cutoff values for nasolacrimal duct obstruction were 0.24, 0.24, 0.17, 0.08, 0.19, and 0.04 cm^3 for V10, V20, V30, V40, V50, and V60, respectively. Indeed, all of these cutoff values classified the obstruction-positive patients with an accuracy above 96%.

Although the cutoff values for V10–V60 all showed excellent performance in predicting nasolacrimal duct obstruction, we here focused on V40 on the basis of its clinical applicability, especially considering our treatment protocol, where the PTV is changed from PTV1 to PTV2 after 36 Gy(RBE). Univariate analysis using the Cox proportional hazards model showed that a high V40 value (i.e., V40 $\geq$0.08 cm^3) is a significant risk factor for nasolacrimal duct obstruction (p = 0.028; hazard ratio: 131.4; 95% confidence interval: 1.6–10278.9; Table 2). Kaplan–Meier analysis showed that the 5 year cumulative incidence of nasolacrimal duct obstruction for the patients with a V40 $\geq$0.08 cm^3 was 93.8%, while that for the patients with a V40 <0.08 cm^3 was 0% (p < 0.001; Fig. 4a). These data indicate the potential clinical usefulness of V40 as a predictive dosimetric parameter for nasolacrimal duct obstruction after carbon-ion radiotherapy.

Table 2
Univariate analysis for risk factors for nasolacrimal duct obstruction.

Parameter	n	p-value	Hazard ratio (95% CI)
V40			
$\geq$0.08 cm^3	16	0.001	131.4 (1.6–10278.9)
<0.08 cm^3	12		
Tumor location			
Nasal cavity or maxillary sinus	15	0.001	29.7 (3.8–231.9)
Others*	13		
Operability			
Operable	12	0.590	1.3 (0.4–3.7)
Inoperable	16		
Carbon-ion dose			
64.0 Gy(RBE)/16 fractions	25	0.644	1.6 (0.2–12.3)
57.6 Gy(RBE)/16 fractions	3		

* Parotid gland, pharynx, oral cavity, and external auditory canal. CI, confidence interval. RBE, relative biological effectiveness.

The univariate analysis also showed that, as expected, the patients who had tumors located in the nasal cavity or maxillary sinus were under significantly higher risk of nasolacrimal duct obstruction than those who had tumors located at other anatomical sites in the head and neck region (p = 0.001; hazard ratio: 29.7; 95% confidence interval: 3.8–231.9; Table 2). Accordingly, Kaplan–Meier analysis showed that the 5 year cumulative incidence of nasolacrimal duct obstruction for patients who had a tumor located in the nasal cavity or maxillary sinus was 93.3%, while the incidence for patients who had tumors located at other anatomical sites in the head and neck region was 7.7% (p < 0.001; Fig. 4b). Of note, inoperable tumors or high total carbon-ion dose was not a risk factor for nasolacrimal duct obstruction in our cohort (Table 2).

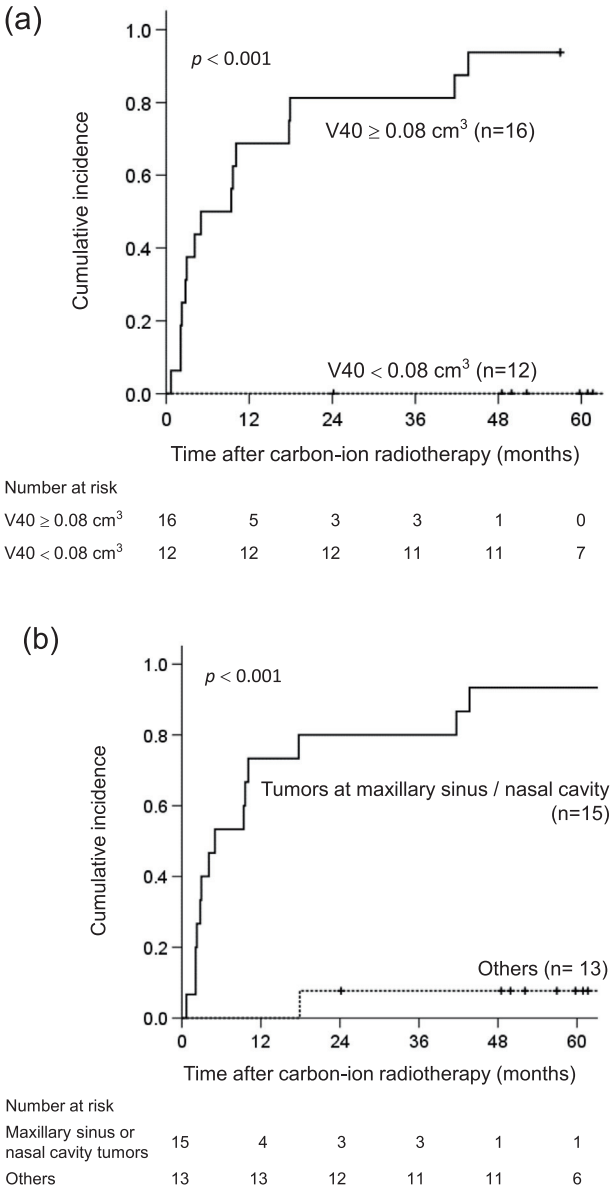

Fig. 4. Cumulative incidence of Grade 1 or higher nasolacrimal duct obstruction stratified by (a) a V40 value of 0.08 cm^3, or (b) primary tumor site. P-values calculated by log-rank test are shown.

Discussion

In this prospective study, we showed that the incidence of nasolacrimal duct obstruction is common in head and neck carcinoma patients undergoing carbon-ion radiotherapy (i.e., 53% of 28 patients), although most of the cases were of Grade 1. We also showed that the volume of the irradiated nasolacrimal ducts has a high capability for classifying obstruction-positive patients throughout the dose range (i.e., V10 through to V60). To the best of our knowledge, this study is the first to report the incidence and risk factors for nasolacrimal duct obstruction after carbon-ion radiotherapy, and our data should be useful for preventing such obstruction after carbon-ion radiotherapy.

While there are no previous studies on nasolacrimal duct obstruction after carbon-ion radiotherapy, there are a limited number of studies on this adverse effect after photon and proton radiotherapy. Truong et al. reported that 10% (2/20) of patients with sphenoid sinus malignancies experienced Grade 2 watering eye after proton therapy (median total dose, 76 Gy equivalent); the adverse effects in the two patients occurred at 7 and 9 months after the therapy, and were salvaged by placement of a nasolacrimal stent [14]. Weber et al. reported that, after radiotherapy treatment using a mixture of photons and protons (median total dose to clinical target volume, 54.4 Gy equivalent) with an accelerated fractionation schedule (i.e., twice a day), 6% (2/36) and 3% (1/36) of patients with advanced sinonasal malignancies experienced Grade 2 or 3 nasolacrimal duct stenosis, respectively [15]. Nakissa et al. reported that 13% (4/30) of patients with paranasal sinus malignancies experienced nasolacrimal duct obstruction after photon radiotherapy, for which a dose of 6572–7500 rad was associated with the adverse event [16], while Son et al. reported that 4% (2/46) of patients with orbital marginal zone B-cell lymphoma experienced nasolacrimal duct obstruction after photon radiotherapy (median total dose, 30.6 Gy) [17]. These data reveal that the incidence of Grade 2 nasolacrimal duct obstruction in our cohort (i.e., 7%) is comparable to that observed after proton radiotherapy performed with curative intent [14,15]. Furthermore, we also report the incidence of Grade 1 nasolacrimal duct obstruction, which was not described in previous reports.

The dose–volume histograms for nasolacrimal ducts in the obstruction-positive patients were distinct from those for the obstruction-negative patients throughout the dose range (Fig. 3). This clearly indicates that nasolacrimal duct obstruction is preventable if appropriate cutoff values are applied in treatment planning. Although all the cutoff values for V10–V60 favorably classified the obstruction-positive patients, we propose V40 with a cutoff value of 0.08 cm^3 for clinical application. This is because the PTV for the treatment is changed from the PTV1 to the PTV2 after 36 Gy(RBE), with PTV1 encompassing the whole anatomic site of the tumor origin (e.g., nasal cavity or maxillary sinus), and PTV2 being based on the tumor. In fact, no patient in our cohort with a V40 <0.08 cm^3 experienced nasolacrimal duct obstruction. Further study is required to validate these results. The diameter of the nasolacrimal duct is approximately 3.5–4.1 mm [18], and on the basis of this measurement, the length of a nasolacrimal duct with a volume of 0.08 cm^3 is calculated to be 6–8 mm. Although it is difficult to meet this constraint for some tumors adjacent to the nasolacrimal duct, these data will be useful information for optimizing the treatment plan for carbon-ion radiotherapy for head and neck tumors.

Several studies have reported dose–volume constraints for carbon-ion radiotherapy. One study reported visual loss after carbon-ion radiotherapy [6,7], although no visual loss was observed in patients whose optic nerves were irradiated with less than 57 Gy(RBE). Visual loss correlated with a delivery of 60 Gy (RBE) to 20% of the volume of the optic nerve. Like the nasolacrimal duct, the optic nerve may be a typical serial organ; thus, this result suggests that a high dose volume is a critical factor in the toxic effect of irradiation delivered by carbon-ion radiotherapy to serial organs, as observed previously for X-ray radiotherapy. Although we think the V40 constraint is clinically useful, it may be possible to identify more useful constraints in higher dose regions. The risk factors for maxillary osteoradionecrosis after carbon-ion radiotherapy were V50 and the presence of teeth within the PTV [6]. The hazard ratio for the presence of teeth within the PTV was higher than for osteoradionecrosis at a dose of V50 (11.3 vs. 1.15). The maxillary bone is not a serial organ; thus, this data suggests that a specific sub-volume is critical for toxicity. The nasolacrimal drainage system from lacrimal puncta consists of the lacrimal canaliculus, the lacrimal sac, and the nasolacrimal duct. Although one or more of these sub-volumes might be more sensitive to irradiation, the effect of irradiation on these sub-volumes could not be evaluated in the present study because their volumes were too small.

The standard treatment for nasolacrimal duct obstruction is dacryocystorhinostomy [19,20]. El-Sawy et al. evaluated the outcomes of dacryocystorhinostomy for head and neck cancer patients treated with high-dose photon radiotherapy, and reported that the symptoms were resolved in 72% of 31 patients (36 eyes) following dacryocystorhinostomy [21]. In their study, the risk for re-obstruction was higher for those patients who developed nasolacrimal duct obstruction within 12 months after the radiotherapy than for those who developed the symptom after 12 months (35%, $\leq$12 months, vs. 21%, >12 months). Their findings are consistent with the results of the present study, i.e., one patient who developed Grade 2 nasolacrimal duct obstruction at 12 months post-therapy had a recurrence of the symptom after dacryocystorhinostomy, while the other patient who developed Grade 2 nasolacrimal duct obstruction at 42 months post-therapy did not experience re-obstruction after dacryocystorhinostomy. These data indicate that dacryocystorhinostomy within the 12 months after carbon-ion radiotherapy may be a predictive factor for the risk of re-obstruction.

A limitation of the present study is the small number of patients included. Validation of the present study with a larger cohort is warranted in the future, and a multi-institutional study is encouraged to overcome the potential shortage of eligible patients.

In conclusion, we demonstrated that a V40 $\geq$0.08 cm^3 is a dosimetric parameter predictive of nasolacrimal duct obstruction. Our data should be useful information for optimizing treatment planning of carbon-ion radiotherapy for head and neck tumors in respect to preventing nasolacrimal duct obstruction.

Declaration of Competing Interest

None.

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