Radiation-induced Parotid Gland Atrophy in Patients with Head and Neck Cancer After Carbon-ion Radiotherapy

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Abstract. *Background/Aim:* This study aimed to clarify the relationship between dosimetric factors and parotid gland (PG) atrophy after carbon ion radiotherapy (C-ion RT). *Patients and Methods:* Fifty-four patients with head and neck tumours were enrolled and 93 irradiated PGs were analyzed. Thirty and 24 patients were treated with total doses [relative biological effectiveness (RBE)] of 57.6 Gy and 64.0 Gy, respectively, in 16 fractions. PG volumes were measured using computed tomographic images obtained before C-ion RT and every 3-6 months thereafter. *Results:* The median follow-up period was 46.4 months (range=24.0-123.0 months). Univariate analysis showed that PG volumes receiving more than 5, 10, 15, and 20 Gy RBE (V5, V10, V15 and V20, respectively), mean dose, and maximum dose were significantly associated with PG atrophy. Multivariate analysis indicated that only V5 was significantly associated with atrophy. *Conclusion:* Increasing V5 was a significant risk factor for PG atrophy after C-ion RT.

Xerostomia is a critical adverse reaction after radiotherapy (RT) for patients with head and neck cancer, and it is associated with dysphagia, dysgeusia, articulatory disorders, and a general worsening of oral hygiene due to aggravation of the intraluminal environment. It can also lead to infection, dental caries, periodontal disease, and respiratory infection (1). The parotid gland (PG) is a major serous gland and the

largest of all the salivary glands. The unstimulated production of saliva by the PG produces approximately 25% of total saliva, which is second only to the submandibular gland, while its stimulated production is the highest, at approximately 60% (2). For RT of head and neck cancer, it is recommended that the mean dose to PGs be below 26 Gy in order to avoid severe xerostomia (2-4).

Carbon ion (C-ion) RT delivers greater relative biological effectiveness (RBE) and a superior dose distribution compared with conventional RT (5, 6). In the head and neck region, C-ion RT is mainly used to treat locally advanced radioresistant tumours, such as adenoid cystic carcinoma, adenocarcinoma, and mucosal malignant melanoma (7). Half of all treated tumours are located in the sinonasal cavity. Prophylactic neck irradiation is not performed because of the lower incidence of regional lymph node metastases compared with that of squamous cell carcinoma. Consequently, severe xerostomia is not usually observed in patients who received C-ion RT because it is easy to reduce the irradiation dose received by the salivary glands. However, we have sometimes experienced PG atrophy with mild xerostomia after C-ion radiotherapy of our patients. There are no clinical data we are aware of regarding PG atrophy after C-ion RT.

This study aimed to clarify the risk factors for PG atrophy after C-ion RT in order to assess the sensitivity of PG to carbon ions.

Patients and Methods

Patient characteristics. From January 2000 to December 2007, a total of 202 patients with locally advanced N0M0 head and neck cancer were treated with C-ion RT at our Institution. Of these, 54 patients with 93 irradiated PGs were enrolled in this study. The inclusion criteria were: i) PG receiving more than 5% of the prescribed dose, ii) a follow-up period of more than 2 years, iii) no history of irradiation or surgery of the PG, and iv) no evidence of local or regional recurrence. Patients with parotid tumours or Sjögren's syndrome were excluded. Patient characteristics are summarized in

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Key Words: Carbon-ion radiotherapy, parotid gland, dose-volume histogram, xerostomia, radiotherapy.

Table I. All patients were re-staged using the seventh edition of the TNM staging system (8). All patients had N0M0 disease.

The treatment protocol for head and neck cancer was reviewed and approved by the National Institute of Radiological Science (NIRS) Ethical Committee on Human Clinical Research, and all patients provided written informed consent. This retrospective study was also reviewed and approved by the NIRS Ethical Committee on Human Clinical Research (no. 16-013).

C-Ion radiotherapy. The C-ion dose is expressed as a photon equivalent dose, i.e. Gy RBE (9), which is defined as the physical dose multiplied by the RBE of C-ions. C-ions have a high linear energy transfer, which is 78 keV/m at the distal portion of the spread-out Bragg peak, assuming a C-ion RBE of 3.0.

Procedure of C-ion radiotherapy. Patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) and immobilized with a low-temperature thermoplastic shell (Shellfitter, Kuraray, Osaka, Japan). Sets of 2.5- or 3.0-mm-thick computed tomographic (CT) images were obtained for treatment planning with immobilization. The clinical target volume (CTV) contained a minimum margin of 5 mm added around the gross tumour volume. In cases of possible tumour invasion to adjacent sites, the CTVs included whole anatomical sites. Prophylactic irradiation to the neck lymph node was not performed. The planning target volume (PTV) contained margins of 2-3 mm added to the CTV. The PGs were not intentionally protected. C-ion RT was administered on a fractionation schedule comprising 64.0 Gy RBE or 57.6 Gy RBE in 16 fractions for 4 weeks, with individual fractions of 3.6 or 4.0 Gy RBE. The target reference point dose was defined at the isocentre, and the PTV was encompassed by the minimum 90% dose line of the reference point dose. Multi-portal irradiation was planned fundamentally to avoid severe normal tissue reactions. Three-dimensional treatment planning was performed using HIPLAN software (NIRS, Chiba, Japan).

Follow-up. The patients were followed-up every 3 months for the first 2 years after C-ion RT and thereafter every 3 to 6 months using CT or MRI. Late radiation-induced xerostomia was assessed by the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring System (RTOG/EORTC) (10).

Volume of PGs and dose-volume histogram (DVH). PGs were manually contoured on each CT image, and all delineations were double-checked. Relationships between PG atrophy and the following DVH parameters were evaluated: mean dose, maximum dose (D_{max}), and percentage of PG volume receiving more than 5 to 60 Gy RBE (V5 to V60). Initial and minimum PG volume data were used for analyses.

Statistics. The Mann-Whitney *U*-test was used to compare initial with minimum PG volume. PGs were divided into two groups, those that decreased in volume and those that did not decrease in volume, according to the median percentage PG volume decrease. Univariate analysis was performed by Mann-Whitney *U*-test to evaluate the relationship between DVH variables and decreases in PG volume. Volume decreases and mean doses were correlated by linear regression. All factors with statistically significant associations in the univariate analysis were included in a multivariate analysis using the Cox proportional hazards model. *p*-Values of less than

Table I. Patient characteristics.

Characteristic	Total
Patients, n	54
Age (range), years	56 (26-79)
Gender, n	
Male,	20
Female	34
Tumour site, n (%)	
Paranasal sinuses	15 (27.8)
Oral cavity	15 (27.8)
Nasal cavity	11 (20.4)
Other	13 (24.0)
Pathology, n (%)	
Adenoid cystic carcinoma	30 (55.6)
Malignant melanoma	10 (18.5)
Adenocarcinoma	7 (13.0)
Squamous cell carcinoma	3 (5.6)
Other	4 (7.3)
T Classification, n	
2	3
3	6
4	38
Unclassified	7

0.05 were considered statistically significant, and all statistical tests were two-sided. All analyses were performed with SPSS software, version 23 (IBM Corp., Armonk, NY, USA).

Results

Thirty patients were treated with a total dose of 57.6 Gy RBE, and 24 patients were treated with a total dose of 64.0 Gy RBE. The median follow-up period was 46.4 months (range=24.0-123.0 months). With regard to xerostomia, 22 patients (40.7%) did not develop xerostomia, 19 (35.2%) had grade 1 xerostomia, and 13 (24.1%) grade 2 xerostomia. Xerostomia higher than grade 3 was not observed during the observation period.

Dose-volume histogram data for PGs. The median mean dose delivered to PGs was 6.7 Gy RBE (range=0.4-41.0 Gy RBE). The median D_{max} was 42.3 Gy RBE (range=9.0-62.0 Gy RBE). Figure 1 displays the mean DVH curves for PGs. The initial and minimum mean volumes of PGs were 26.3 cc (range=15.2-52.6 cc) and 20.6 cc (range=9.4-44.5 cc), respectively. The volume of PGs after C-ion RT significantly decreased compared to that before C-ion RT ($p<0.001$). When decreases in PG volumes were correlated with mean doses to the PG in linear regression analysis, a statistically significant relationship was found ($y=0.5011x + 16.646$, $r=0.294$, $p=0.004$) (Figure 2). The median volume decrease was 18.7% (range=0.1-57.5%). The period between treatment initiation

Figure 1. Mean dose-volume histogram of the 93 parotid glands. Data are the mean $\pm$ 2SE. RBE: Relative biological effectiveness.

Figure 2. Volume decrease of parotid glands upon completing carbon-ion radiotherapy versus the initial gland volume as a function of the mean dose for all parotid glands. The dotted line displays the linear regression ($r=0.294$, $p=0.004$). Pearson's correlation coefficient method was used to calculate an equation for the regression line, $y=0.5011x + 16.646$.

and the time at which the volume was smallest ranged from 1.0 to 23.0 months, with a median of 6.0 months.

Univariate and multivariate analyses of volume decrease. The 93 PGs were divided into two groups: the volume decrease group, which consisted of 46 PGs with $\geq 18.7\%$ volume decrease, and the non-volume decrease group, which consisted of 47 PGs with $< 18.7\%$ volume decrease. Figure 3 shows the mean DVHs for each group. Univariate analysis showed that V5, V10, V15, V20, mean dose, and $D_{\max}$ were significant prognostic factors of PG volume decrease. Multivariate analysis indicated that only V5 was significantly associated with PG volume decrease ($p=0.013$, hazard ratio=1.042, 95% confidence interval=1.009-1.076; Table II).

Figure 3. The curves display the mean dose-volume histograms of the non-volume decrease group (below 18.7% decrease in parotid gland volume) and the volume decrease group (18.7% or more decrease in parotid gland volume).

Discussion

The mean dose to the PG is a predictive factor for severe xerostomia in patients undergoing radiotherapy. Intensity-modulated radiotherapy (IMRT) for head and neck cancer can spare PGs, leading to significant reductions in the incidence and severity of xerostomia, at a mean dose to PGs of approximately 26 Gy (11-15). Moreover, salivary function tends to recover within 2 years of IMRT if the mean dose to the PG is 30 Gy or less (12). Anand *et al.* noted a relationship between the mean dose and frequency of xerostomia using a questionnaire and objective toxicity observations. The mean dose to a unilateral PG should be below 35 Gy to reduce the frequency of grade 3 xerostomia (16).

Prophylactic lymph node irradiation was usually not performed in C-ion RT because of the lower incidence of regional lymph node metastases in patients with eligible tumours compared to that of squamous cell carcinoma. Consequently, several salivary glands were completely spared, and volume decreases of irradiated PGs were not necessarily associated with severe xerostomia. In this study, no patients developed grade 3 xerostomia although the mean volume decrease of irradiated PGs was 21.7%.

A few studies have reported a relationship between PG volume decreases and dosimetric parameters. Wang *et al.* reported a relationship between decreased PG volume and three levels of the irradiation doses to the PGs after conventional RT for head and neck cancer: low (< 30 Gy) in 78 PGs, medium (30-50 Gy) in 37 PGs, and high (> 50 Gy) in 47 PGs. The PG volume decrease correlated significantly with mean dose to the irradiated PGs (17). In our study, the mean dose was a predictive factor of PG volume decrease

Table II. Univariate and multivariate analyses of factors that predict decrease in the volume of parotid glands (PGs) after carbon-ion radiotherapy.

	Non-volume decrease/ volume decrease	Univariate analysis	Multivariate analysis		
		p-Value	Hazard ratio	95% CI	p-Value
Number of PGs	47/46				
Dose-volume histogram parameter					
Mean V5, (%)	41.0/65.4	<0.001	1.042	1.009-1.076	0.013
Mean V10, (%)	23.6/48.3	0.001	1.012	0.960-1.066	0.669
Mean V15, (%)	15.3/32.1	0.012	1.019	0.920-1.128	0.720
Mean V20, (%)	12.5/25.3	0.022	0.979	0.870-1.101	0.718
Mean V25, (%)	9.3/14.4	0.265			
Mean V30, (%)	4.6/7.8	0.294			
Mean V35, (%)	3.7/5.6	0.483			
Mean V40, (%)	2.7/3.9	0.547			
Mean V45, (%)	2.0/3.2	0.484			
Mean V50, (%)	1.0/2.3	0.203			
Mean V55, (%)	0.7/1.7	0.183			
Mean V60, (%)	0.0/0.4	0.060			
Mean dose, (Gy RBE)	6.8/11.7	0.006	0.888	0.695-1.135	0.343
D _{max} , (Gy RBE)	26.9/37.8	0.006	0.076	0.992-1.076	0.119

RBE: Relative biological effectiveness; Vn: percentage of parotid gland volume receiving more than the dose n Gy RBE; D_{max}: maximum dose; CI: confidence interval.

by univariate analysis. However, V5 was the only notable independent significant predictive factor in multivariate analysis. Thus far, no study that has mentioned such a low dose for the preservation of salivary glands in a clinical setting. However, Wang *et al.* showed that a mean dose ranging from 10-20 Gy reduced the volume of the PGs in the study above (17). In an *in vivo* setting using rhesus monkeys, Stephens *et al.* reported atrophy of PGs after irradiation, as a direct result of acute loss of serous acini. Additionally, loss of PG acini was minimal with doses of 5.0 and 7.5 Gy, although the doses were delivered in a single fraction (18).

In general, PGs are known to be radiosensitive organs. However, the RBE for the PG in C-ion RT is unclear. Wang *et al.* also demonstrated a linear relationship between the loss of PG volume after conventional RT (y) and the mean dose to the PG (x) ($y=17.156+0.24x$, $r=0.405$, $p<0.001$) (17). A mean dose of 32.7 Gy resulted in a 25% volume decrease. In our study, a mean dose of 14.3 Gy RBE resulted in a 25% volume decrease, although the accuracy of our linear regression was not high enough for analysis ($r=0.294$, $p=0.004$). However, these data suggest the RBE for the PG in C-ion RT may possibly be around 7 instead of 3.

C-ion RT can easily accomplish conformal distribution of physical characteristics, such as a Bragg peak and small lateral scattering (5, 6). Recently, we introduced a new irradiation technique, spot scanning irradiation, which can reduce the irradiated dose to the area proximal of the tumour,

compared to the dose received with passive irradiation (19). In addition, a rotating gantry will be available in the near future. These new technologies will potentially improve the dose distribution of C-ion RT, particularly for low and medium dose areas.

The present study had several limitations. Firstly, there are no data concerning the relationship between PG volume decreases and saliva output, although the residual gland volume after RT and radiation dose to the gland are crucial for recovery of gland function and saliva output. Secondly, we did not consider the recovery of PG volume in this study, we used the minimum volume of PG for analysis. There are several articles that have shown recovery of saliva output 2 years after RT if the radiation dose was <30 Gy. However, they report no data on the recovery of PG volume after RT.

Xerostomia is not a common adverse reaction to C-ion RT for head and neck cancer because of the unique patient populations and its superior dose distribution. This study suggests that a lower dose of C-ion RT might affect the function of the PG, compared to that of conventional RT. In order to improve the quality of life of patients treated with C-ion RT, we must pay close attention to the PG volume that is irradiated by the low dose.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in regard to this study.

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