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Structural Variations in Parotid Glands Induced by Radiation Therapy in Patients with Oral Carcinoma Observed on Contrast-Enhanced Computed Tomography

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Xerostomia is one of the commonest radiation-induced complications in patients with head and neck carcinoma. The aim of this study was to assess structural variations in parotid glands induced by radiation therapy in patients with oral carcinoma with contras-enhanced computed tomography (CECT).

Material/Methods: A retrospective study was performed in 41 patients with oral carcinoma who underwent CECT for head and neck malignancies before and after radiotherapy. We analyzed the relationship between parotid density variations, parotid volume change, as seen on CECT, and the mean radiation dose applied to the parotid glands in patients with oral carcinoma immediately after radiotherapy, and 2 and 3 years later.

Results: Immediately after radiotherapy, high-density changes on contrast-enhanced CT were observed in 70.5% of the irradiated parotids. Low-density changes due to fat degeneration were seen in 46.2% and 72.2% of the irradiated parotids 2 and 3 years after radiotherapy, respectively. The mean dose applied to the parotids with the low-density changes and without such changes 3 years after radiotherapy was 46.0 Gy and 27.7 Gy, respectively (p=0.049). Furthermore, parotid shrinkage was observed in 63.6% of the irradiated parotids.

Conclusions: This study suggests that the structural variations in parotid glands induced by radiotherapy included high-density changes that were observed immediately after radiotherapy and low-density changes that were seen at late follow-up. This study should be useful for clinicians in the assessment of radiation-induced injuries in the parotids with respect to early prediction of xerostomia.

MeSH Keywords: Head and Neck Neoplasms • Multidetector Computed Tomography • Parotid Gland • Radiotherapy • Xerostomia

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Background

Radiotherapy has played an important role in the treatment of patients with head and neck cancer, despite the risk of side-effects [1]. Xerostomia is one of the commonest radiation-induced complications in patients with nasopharyngeal carcinoma after a radical course of radiotherapy [2]. Persistent xerostomia, due to damage of the parotid glands, causes difficulties in mastication and swallowing and degrades the quality of life in long-term survivors [3,4].

With the recent advancements in radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), highly conformal dose distributions are possible, and sparing of the parotid gland is more effective [1,5]. However, conventional radiotherapy protocols for nasopharyngeal cancers are still used in some centers. This treatment protocol employs lateral opposing beams to the face and upper neck together with an anterior beam to cover the lower neck [6].

To date, the mechanism of parotid gland damage and saliva reduction due to radiation is largely unknown [6]. It is postulated that secretion of saliva secretion by the parotid glands is related to the changes in morphology and vascularity that are induced by radiotherapy [7]. Contrast-enhanced computed tomography (CECT) is a useful imaging tool for monitoring the response to radiotherapy, and it provides morphological information of the head and neck structures, including the parotid glands. However, the structural variations in the parotid glands induced by radiation therapy in patients with oral carcinoma are still not well studied. The topic of this study is currently of interest with respect to the assessment of radiation-induced injuries in the parotids, especially regarding early prediction of xerostomia. The aim of this CECT-based study was to assess structural variations in the parotid glands induced by radiation therapy that could aid in early prediction of xerostomia in patients with oral carcinoma.,

Material and Methods

Patients

This retrospective study was approved by the ethics committee of our institution. After providing written informed consent, 41 patients (24 male and 17 female, age range 35-89 years, mean age 68.0 years) with oral carcinoma (tongue: 12 patients, buccal mucosa: 9 patients, maxilla: 9 patients, mandible: 5 patients, floor of the mouth: 5 patients, lip: 1 patients) underwent CECT of the head and neck before and after radiotherapy in our university hospital from January 2008 to March 2016.

Radiotherapy

Conventional two portal, opposing field irradiation was performed with a linear accelerator (Primus; Toshiba Medical Systems, Otawara, Japan). Treatment planning was performed with a 3D treatment planning system (Xio; CMS JAPAN, Tokyo, Japan). The radiotherapy protocol used 4MV photons and involved irradiation of the parotid glands. Preoperative radiotherapy was performed in 14 patients, and the total dose applied to the tumor was 26–40 Gy, delivered in 2-Gy daily fractions. Radical radiotherapy was performed in 27 patients, and the total dose applied to the tumor was 50–72 Gy, delivered in 2-Gy daily fractions. The period of follow-up ranged between 13 and 97 months (mean 51.0 months).

Image acquisition

CT imaging was performed with a 16-multidetector CT scanner (Aquilion TSX-101A; Toshiba Medical Systems, Otawara, Japan). We used the protocol for oral cancer routinely applied in our hospital, as follows: tube voltage, 120 kV; tube current, 300 mA; field of view, 240×240 mm; and rotation time, 0.5 s. All patients underwent CECT with nonionic iodine contrast. We used the following nonionic contrast agent: Iohexol 300 mgI/mL (Omunipaque 300 Syringe, Daiichi-Sankyo, Tokyo, Japan). The contrast agent was administered as an injection (100 ml), at a rate of 2.0 mL/s (Autoenhance A-250, Nemoto-Kyorindo, Tokyo, Japan).

Image analysis

The relationship between parotid density variations and parotid volume changes, as seen on CECT, and the mean dose applied to the parotids (as assessed by our 3D treatment planning system) was analyzed in 44 parotid glands in (all 41 patients with oral carcinoma) immediately after radiotherapy, and 2 and 3 years later. We performed a quantitative analysis based on CT data on the amount of high- and low-density variations. We performed a quantitative analysis with respect to the size of the parotid glands. Furthermore, the following prognostic factors of density variations after 3 years of follow-up and volume changes in the parotid glands on CECT were evaluated: age, gender, mean dose applied to the parotids, and high-density changes immediately after radiotherapy.

Statistical methods

The relationship between density variations and volume changes in the parotid glands (seen on CECT) induced by radiotherapy, and the mean dose applied to the parotids in patients with oral carcinoma was compared with the Mann-Whitney U test for nonparametric data. The prognostic factors of density variations after 3 years of follow-up and volume changes in the parotid glands on CECT were evaluated with logistic multivariate regression analysis with respect to CECT findings, age, gender, mean dose applied to the parotids, and high-density changes immediately after radiotherapy. These analyses were performed with the IBM SPSS Statistics statistical package, version 24 (IBM Japan, Tokyo, Japan). A P value lower than 0.05 was considered as statistically significant.

Results

The percentage of male patients in the preoperative and radical groups were 25.0% and 75.0%, respectively (Table 1). As regards the percentage of primary tumors in the preoperative and radical groups, there were 20.0% and 80.0% of patients with floor of the mouth carcinoma, and 22.2% and 77.8% of patients with the maxillary carcinoma,

Table 1. Correlation of oral carcinoma patients' characteristics with course of irradiation.

Parameter	Course of irradiation		
	Preoperative radiotherapy	Radical radiotherapy	Total
Number of patients with oral carcinoma	14 (34.1%)	27 (65.9%)	41 (100%)
Age (years)			
Range	44–79	35–89	35–89
Mean	65.1	69.5	68.0
Gender			
Male	6 (25.0%)	18 (75.0%)	24 (100%)
Female	8 (47.1%)	9 (52.9%)	17 (100%)
Primary tumour			
Tongue	6 (50.0%)	6 (50.0%)	12 (100%)
Buccal mucosa	3 (33.3%)	6 (66.7%)	9 (100%)
Maxilla	2 (22.2%)	7 (77.8%)	9 (100%)
Mandible	2 (40.0%)	3 (60.0%)	5 (100%)
Floor of mouth	1 (20.0%)	4 (80.0%)	5 (100%)
Lip	0 (0%)	1 (100%)	1 (100%)
Radiation dose of primary tumour			
Range	26–40 Gy	50–72 Gy	26–72 Gy
Mean	32.4 Gy	64.1 Gy	53.3 Gy

Table 2. Relationship between density variations and volume changes in parotid glands induced by radiotherapy of oral carcinoma on CECT and mean dose to the parotids.

Structural variations in parotid glands on CECT	Number of parotids	Radiation dose to the parotid gland (Gy)			
		Mean ±SD	Range	Median	P value
Density variations					
Immediately after radiotherapy	44 (100%)				0.079
High density changes	31 (70.5%)	46.8±22.3	4–70	60.0	
No changes	13 (29.5%)	35.2±20.6	7–66	30.0	
At 2 years of follow-up	39 (100%)				0.049
Low density changes	18 (46.2%)	49.4±21.2	8–70	60.0	
No changes	21 (53.8%)	33.7±21.2	4–68	30.0	
At 3 years of follow-up	36 (100%)				0.049
Low density changes	26 (72.2%)	46.0±20.4	8–70	51.0	
No changes	10 (27.8%)	27.7±24.4	4–68	22.0	
Volume changes	44 (100%)				0.240
Parotid shrinkage	28 (63.6%)	46.3±23.3	4–70	56.0	
No changes	16 (36.4%)	38.3±20.0	7–68	31.5	

CECT – contrast enhanced CT; SD – standard deviation.

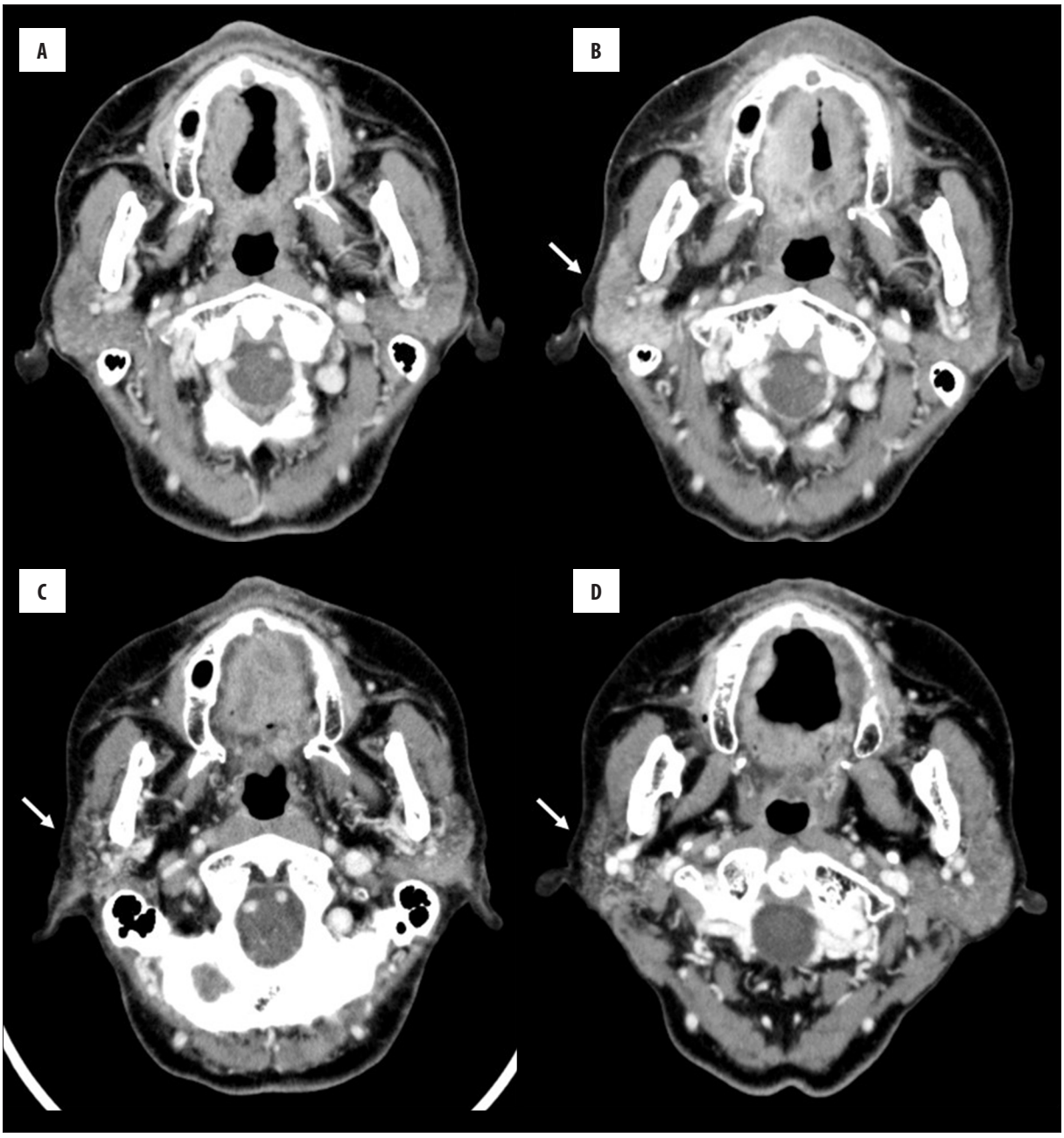

Figure 1. A 70-year-old female with right-sided maxillary carcinoma after radical irradiation (total 66Gy). Radiation dose applied to the right and left parotid glands was 20 Gy and 0 Gy, respectively. (**A**) CT before radiotherapy shows no difference between the right and left parotid glands. (**B**) Contrast-enhanced CT performed immediately after radiotherapy shows high-density changes in the right parotid gland (arrow). (**C**) CT performed 2 years after radiation therapy shows low-density changes (fat degeneration) and parotid shrinkage in the right parotid gland (arrow). (**D**) CT performed 3 years after radiation therapy shows low-density changes (fat degeneration) and parotid shrinkage in the right parotid gland (arrow).

respectively. The radiation dose in the radical group (mean dose of 64.1 Gy) was higher than that in the preoperative group (mean dose of 32.4 Gy). As regards the dose applied to the parotid glands, 44 parotid glands of all 41 patients were irradiated for oral carcinoma. The mean dose (± standard deviation) applied to the parotids was 43.4±22.2 Gy (dose range 4–70 Gy, median dose 44.0 Gy).

Immediately after radiotherapy, the percentage of high-density changes on contrast-enhanced CT was 70.5% (Table 2, Figure 1A, 1B). The mean dose applied to the parotids with high-density changes and to the parotid with no changes was 46.8 Gy and 35.2 Gy, respectively (p=0.079). The percentage of low-density changes, i.e., fat degeneration, on CT in the parotids 2 years after radiotherapy was 46.2% (Figure 1C). The mean dose applied to the parotids with low-density changes and to the parotids with no changes was 49.4 Gy and 33.7 Gy, respectively (p=0.049). The percentage of low-density changes, i.e., fat degeneration, seen in the parotids 3 years after

Table 3. Logistic multivariate regression analysis of the prognostic factors in density variations in parotid glands at 3 years of follow-up on CECT.

Prognostic factor	Odds ratio	95% CI	P value
Age	1.063	0.980–1.154	0.142
Gender	0.817	0.138–4.849	0.824
Mean dose to the parotids	1.043	1.002–1.086	0.040
High density changes at immediately after radiotherapy	0.847	0.151–4.741	0.850

CECT – contrast enhanced CT; CI – confidence interval.

Table 4. Logistic multivariate regression analysis of the prognostic factors in volume changes in parotid glands on CECT.

Prognostic factor	Odds ratio	95% CI	P value
Age	1.031	0.969–1.097	0.335
Gender	1.018	0.260–3.983	0.980
Mean dose to the parotids	1.012	0.981–1.043	0.465
High density changes at immediately after radiotherapy	2.353	0.582–9.517	0.230

CECT – contrast enhanced CT; CI – confidence interval.

radiotherapy was 72.2% (Figure 1D). The mean dose applied to the parotids with low-density changes and to the parotids with no changes was 46.0 Gy and 27.7 Gy, respectively (p=0.049). Parotid shrinkage was seen in 63.6% of the parotids after radiation therapy (Figure 1C, 1D). The mean dose applied to the parotids with shrinkage and to the parotids without shrinkage was 46.3 Gy and 38.3 Gy, respectively (p=0.240).

The data showed a significant relationship between density variations and the mean dose applied to the parotids (Table 3, odds ratio=1.043, p=0.040). The data showed a relationship between volume changes and high-density changes immediately after radiotherapy (Table 4, odds ratio=2.353, p=0.230).

Discussion

Salivary glands are usually irradiated during radiotherapy for head and neck cancers, which can lead to radiation-induced damage [8]. CT is the most frequently used imaging procedure for staging and post-therapeutic follow-up of patients with head and neck tumors. This CECT-based study investigated the structural variations in the parotid glands induced by radiation therapy for oral carcinoma. In this study, the structural variations in the parotid glands induced by radiotherapy for oral carcinoma included high-density changes on contrast-enhanced CT (immediately after radiotherapy) and low-density changes, i.e., fat degeneration (long-term follow-up).

Post-radiotherapy parotid glands demonstrated loss of gland parenchyma and acinar cell atrophy [9], which was responsible, in part, for the more heterogeneous, variable hyperechocity that appeared in the ultrasound scan [7] and gland volume shrinkage in CT images [6] in the cited studies. It is generally accepted that radiation therapy in patients with head and neck cancer causes salivary gland destruction, inevitably leading to radiation-induced xerostomia [10]. In this study, the percentage of low-density changes (fat degeneration) seen on CT was 72.2% of all irradiated parotids after 3 years of follow-up. The mean dose applied to the parotids with low-density changes and to the parotid with no changes was 46.0 Gy and 27.7 Gy, respectively. Furthermore, logistic multivariate regression analysis of the prognostic factors showed a significant relationship between density variations and the mean dose applied to the parotids. We consider that higher radiation doses applied to the parotid glands cause greater loss and atrophy of acinar cells. The atrophy of the acinar cells must be the main cause of impaired salivary secretion leading to xerostomia. Teshima et al. [11] suggested that acinar cell loss is the main contributor to changes in the volume and function of irradiated human parotids and submandibular glands, and the CT density value may reflect the adipose ratio rather than salivary function. We believe that time-dependent changes that are observed on CT are in accordance with the timing of pathological changes of an acute inflammatory reaction followed by the development of progressive fibrotic changes.

As regards volume changes in the parotid glands induced by radiotherapy, Wu et al. [6] showed that the post-radiotherapy parotid gland volumes in all patients were smaller than those of the pre-radiotherapy glands. We showed that the percentage of parotid shrinkage was 63.6% of all irradiated parotids.

In this study, the percentage of high-density changes observed on contrast-enhanced CT was 70.5% immediately after radiotherapy. Furthermore, the mean dose applied to the parotids with high-density changes and to the parotids with no changes was 46.8 Gy and 35.2 Gy, respectively. As regards the assessment of post-radiotherapy vascular changes of the parotid glands, dose-dependent increases in the extracellular extravascular space,

and decreases in vascular permeability were reported on MRI [12]. Belli et al. [13] showed that parotid gland volume and density changes were observed mostly during the first part of radiotherapy. We consider that the parotid glands, immediately after irradiation, were characterized by high-density changes on contrast-enhanced CT, as early radiation-induced injuries of the parotid glands are known as acute radiation parotitis [11]. Furthermore, Imanimoghaddam et al. [14] showed the ultrasonographic changes of the parotid and submandibular glands in patients undergoing radiotherapy for head and neck malignancies. Scalco et al. [15] analyzed the usefulness of texture analysis for the assessment of structural changes in the parotid glands induced by radiotherapy that can be seen on CT. Marzi et al. [16] reported that early changes in irradiated major salivary glands can be noninvasively evaluated by intravoxel incoherent motion MRI. In recent years, density variation of parotid glands during IMRT for head and neck cancer [17,18] and radiation-induced CT density changes in the parotid glands [19,20] have been reported in the literature. The authors consider that the relation between multimodal imaging, such as CT, MRI ultrasonography, and xerostomia could be important for subsequent research.

The limitations of this study were as follows: the number of patients with oral carcinoma after radiation therapy was small. Furthermore, no effort was devoted to searching for the correlation between the observed changes and treatment outcome, which could be important to understand the mechanism of radiation-induced damage in the parotid glands. It would be very interesting to investigate the correlation between structural variations of the parotid glands, that can be observed on CECT, and xerostomia score.

Conclusions

This CECT-based study found that the structural variations in the parotid glands induced by radiation therapy included high-density changes (immediately after radiotherapy) and low-density changes (long-term follow-up). The topic addressed in this study is currently of interest for the assessment of radiation-injuries in the parotids, especially with respect to early prediction of xerostomia. This study could contribute to elucidating the correlation between xerostomia and the presence of radiotherapy-induced structural variations on CECT in patients with oral carcinoma

Conflict of interest

We declare no financial support or relationship that may pose conflict of interest.

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