Longitudinal Changes over 2 Years in Parotid Glands of Patients Treated with Preoperative 30-Gy Irradiation for Oral Cancer

Etsushi Tomitaka1, Ryuji Murakami2,*, Keiko Teshima3, Tomoko Nomura2, Yuji Nakaguchi2, Hideki Nakayama3, Mika Kitajima4, Toshinori Hirai4, Yushi Araki1, Masanori Shinohara3 and Yasuyuki Yamashita4

1Department of Radiology, National Hospital Organization Kumamoto Medical Center, 2Department of Medical Imaging, Faculty of Life Sciences, Kumamoto University, 3Department of Oral and Maxillofacial Surgery, Faculty of Life Sciences, Kumamoto University and 4Department of Diagnostic Radiology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

*For reprints and all correspondence: Ryuji Murakami, Department of Medical Imaging, Faculty of Life Sciences, Kumamoto University, 4-24-1 Kuhonji, Kumamoto 862-0976, Japan. E-mail: murakami@kumamoto-u.ac.jp

Received October 11, 2010; accepted December 7, 2010

Objective: To evaluate longitudinal changes in parotid volumes and saliva production over 2 years after 30 Gy irradiation.

Methods: We retrospectively evaluated 15 assessable patients treated for advanced oral cancer. Eligibility criteria were a pathologic diagnosis of squamous cell carcinoma, preoperative radiation therapy with a total dose of 30 Gy delivered in 15 fractions, and the availability of longitudinal data of morphological assessments by computed tomography and functional assessments with the Saxon test spanning 2 years after radiation therapy. In the Saxon test, saliva production was measured by weighing a folded sterile gauze pad before and after chewing; the low-normal value is 2 g/2 min. Repeated-measures analysis of variance with Bonferroni adjustment for multiple comparisons was used to determine the longitudinal changes.

Results: The normalized ipsilateral parotid volumes 2 weeks and 6-, 12- and 24 months after radiation therapy were found to be 72.5, 63.7, 66.9 and 78.1%, respectively; the normalized contralateral volumes were 69.8, 64.6, 72.2 and 82.0%, respectively. The bilateral parotid volumes were significantly decreased after radiation therapy ($P < 0.01$). The nadir appeared at 6 months post-radiation therapy and the volumes substantially recuperated 24 months after radiation therapy ($P < 0.01$). Mean saliva production before radiation therapy was 3.7 g; the longitudinal changes after radiation therapy were 31.3, 38.0, 43.3 and 69.6%, respectively. Substantial recuperation of saliva production was observed 24 months after radiation therapy ($P = 0.01$).

Conclusions: Although parotid volumes and saliva production were decreased after 30 Gy irradiation, we observed the recuperation of morphological and functional changes in the parotid glands 2 years after radiation therapy.

Key words: radiation therapy – xerostomia – saliva – parotid gland

INTRODUCTION

Xerostomia is a common debilitating adverse effect of radiation therapy (RT) in patients with head-and-neck tumors (1). Saliva production is reduced after the delivery of 10–15 Gy to the parotid gland (2,3) and although functional recuperation over time is possible after irradiation with 40–50 Gy, higher doses produce irreversible and permanent xerostomia (4–7). To spare glandular function, the recommended mean dose to the parotid glands is $< 25–30$ Gy (8–12).

Eisbruch et al. (8), who measured the salivary flow up to 12 months after RT, recommended that treatment planning should include the delivery of a mean dose of $< 26$ Gy to
the parotid gland. Portaluri et al. (9) followed their patients at least 16 months; they reported that patients with no or mild xerostomia had received a mean dose of approximately 30 Gy to the contralateral parotid gland. In their study on radiation-induced damage to the parotid glands and their functional recovery, Li et al. (10) found that in patients treated with doses below 25–30 Gy, the saliva production returned to pretreatment levels after 2 years.

Although there are many studies on the functional changes in irradiated parotid glands, reports on parotid volumes are limited (13–19). Elsewhere we documented a mean parotid volume ratio of 71% after 30 Gy irradiation and a correlation between decreased parotid volume and decreased saliva production in patients with advanced oral squamous cell carcinoma (SCC) (20). However, longitudinal data on parotid volume changes were lacking. Therefore, we followed patients who had received preoperative conventional 30 Gy irradiation for at least 2 years and recorded longitudinal changes in parotid volumes and saliva production.

PATIENTS AND METHODS

A prior informed written consent for routine Saxon tests and treatment was obtained from all patients. The institutional review board of our hospital approved this investigation.

PATIENT CHARACTERISTICS

We retrospectively evaluated 15 assessable patients (11 men and 4 women; mean age: 67 years, age range: 54–86 years) with advanced oral cancer. Eligibility criteria were a pathologic diagnosis of SCC, preoperative chemo-RT with a total dose of 30 Gy delivered in 15 fractions, absence of recurrence and the availability of longitudinal data, including morphological assessments by computed tomography (CT) and functional assessments with the Saxon test before- and 2 weeks and 6-, 12- and 24 months after 30 Gy irradiation. The Saxon test measures saliva production by weighing a folded sterile gauze pad before- and 2 min after chewing without swallowing; the low-normal value is 2 g (20,21). Of the 15 patients, 3 had maxillary gingival-, 5 had mandibular gingival-, 1 each had a palate- and a buccal mucosa-, 2 had tongue- and 3 had oral floor tumors; all had received preoperative chemo-RT between April 2005 and December 2007. Clinically, four patients had T2-, three had T3- and eight had T4 tumors; nodal involvement was N0 in five-, N1 in two-, N2b in five- and N2c in three patients.

Our preoperative chemo-RT protocol (22) delivers a total dose of 30 Gy at daily fractions of 2 Gy over the course of 3 weeks using a 4 MV linear accelerator with opposed lateral fields. The primary tumor and nodal levels suspected of metastatic involvement were included in the clinical target volume; ipsi- and contralateral parotid glands were similarly included in irradiated volume. On the basis of a dose-volume histogram analysis in the 15 patients, the mean dose to the ipsi- and contralateral parotid glands (mean ± SD) were 29.1 ± 1.5 Gy and 29.0 ± 1.6 Gy. Concurrently, S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was administered orally at a daily dose of 80 mg/m² starting on the first day of RT and continuing for two consecutive weeks. S-1 is a novel oral fluoropyrimidine preparation; it is designed to improve the antitumor activity of 5-fluorouracil while reducing gastrointestinal toxicity (22).

The response 2 weeks after the completion of preoperative chemo-RT was evaluated clinically and radiologically, and surgical resection with reconstruction was performed 3–4 weeks after the chemo-RT. Radical en bloc resection was based on the degree of tumor extension determined before chemo-RT. The involved area, including a planned safety margin, was marked by an ink tattoo. Neck dissection was performed depending on nodal staging. In all patients except one, the ipsilateral submandibular gland was resected at the surgery. The ipsilateral sublingual gland was also resected in five patients. For follow-up evaluation, the patients were seen on an outpatient basis at every 2–4 weeks during the first year after surgical resection, and at 1–6 month intervals thereafter. The patients also underwent follow-up CT studies every 3–6 months.

PAROTID VOLUMES

Longitudinal CT data on the head-and-neck were transferred to a 3D-radiotherapy planning system (RTPS, Pinnacle3 8.0d; Philips Medical Systems, Fitchburg, MA, USA) using the digital imaging and communications in medicine format. The parotid volumes on CT were consensually assessed and manually contoured by two observers: a radiologist (M.K.) and a DDS (T.N.) with 15 and 7 years of experience in diagnosing and treating oral cancers, respectively. They were blinded to the Saxon test results and to the presence or absence of xerostomia. The ipsi- and contralateral parotid volumes before- and 2 weeks and 6-, 12- and 24 months after 30 Gy irradiation were retrospectively measured and recorded for each patient.

STATISTICAL ANALYSIS

Original data were converted to fractions of the baseline values (normalized saliva production and parotid volume) because there were considerable individual variations (20). We used the repeated-measures analysis of variance (ANOVA) with Bonferroni adjustment for multiple comparisons to evaluate longitudinal changes in morphological and functional data. The relationship between saliva production and parotid volume was evaluated with the Pearson correlation test. Statistical analyses were carried out with the MedCalc program (version 9.2.1.0; MedCalc Software, Mariakerke, Belgium). For all analyses, values of P < 0.05 were considered to denote significant differences.
RESULTS

The ipsi- and contralateral parotid volumes (mean ± SD) before 30 Gy irradiation were 32.3 ± 6.0 and 33.4 ± 6.3 cm³, respectively. The normalized ipsilateral parotid volumes 2 weeks and 6-, 12- and 24 months after 30 Gy irradiation were 72.5, 63.7, 66.9 and 78.1%, respectively. The nadir appeared at 6 months post-RT and the volumes substantially recuperated 24 months after RT \( (P < 0.01) \). W, weeks; M, months.

Figure 1. Normalized ipsilateral parotid volumes in patients treated with radiation therapy (RT) for oral cancer. The mean volumes 2 weeks and 6-, 12- and 24 months after 30 Gy irradiation were 72.5, 63.7, 66.9 and 78.1%, respectively. The nadir appeared at 6 months post-RT and the volumes substantially recuperated 24 months after RT \( (P < 0.01) \). W, weeks; M, months.

The normalized contralateral parotid volumes 2 weeks and 6-, 12- and 24 months after RT were 72.5 ± 12.2, 63.7 ± 10.4, 66.9 ± 9.6 and 78.1 ± 12.5%, respectively (Fig. 1). The normalized contralateral volumes were 69.8 ± 11.9, 64.6 ± 13.2, 72.2 ± 9.0 and 82.0 ± 11.2%, respectively (Fig. 2). The bilateral parotid volumes were significantly decreased after RT \( (P < 0.01) \), repeated-measures ANOVA with Bonferroni adjustment). The nadir appeared 6 months after RT and the volumes substantially recuperated 24 months after RT \( (P < 0.01) \) (Fig. 3). Mean saliva production before RT was 3.7 ± 1.9 g; the longitudinal changes 2 weeks and 6-, 12- and 24 months after RT were 31.3 ± 16.8, 38.0 ± 18.0, 43.3 ± 26.1 and 69.6 ± 33.4%, respectively (Fig. 4). In saliva production, the nadir appeared 2 weeks after RT; substantial recuperation was observed 24 months after RT \( (P = 0.01) \); at 2.4 ± 1.3 g, mean saliva production was at the normal level. Although there were considerable individual variations, in all patients the normalized total parotid volumes were correlated with normalized saliva production \( (r = 0.36, P = 0.01; \) the Pearson correlation test) at all assessed post-treatment intervals except 2 weeks after RT (Fig. 5). To eliminate the potential effects of radiation-induced inflammatory changes, we excluded the data acquired 2 weeks after RT from our analysis of the relationship between saliva production and parotid volume.

DISCUSSION

The patients with xerostomia should receive oral care to prevent mucositis, dental caries, oral infection, difficulty
No¨mayr et al. (17) reported that the parotid volume loss during conventional RT was 0.6%/day of the initial volume for at least 2 years after RT. To estimate the potential effects of radiation-induced inflammatory changes, data acquired 2 weeks after RT were excluded from this analysis. The Pearson correlation coefficient was 0.36 ($P = 0.01$).

Our evaluation of longitudinal changes in saliva production and parotid volumes in patients treated with 30 Gy irradiation for oral cancer showed that their saliva production and parotid volumes substantially recuperated at 24 months post-RT; they should receive oral care for at least 2 years after RT.

According to Barker et al. (15), median parotid volume loss during conventional RT was 0.6%/day of the initial volume. Nömayr et al. (17) reported that the parotid volume was reduced by approximately 26 and 40% after 30 and 70 Gy irradiation, respectively, and Robar et al. (18) found gland shrinkage of 4.9% per week in patients subjected to intensity-modulated RT (IMRT). Similarly, Bhide et al. (19) demonstrated a reduction in volume of 31% by week 4 in patients subjected to chemo-RT with IMRT. Our previous study (20) and current studies suggested that the parotid volumes after 30 Gy irradiation were approximately 70% of the baseline values. Our present study also documents that the parotid volume gradually recuperated in the course of 2 years post-RT and that the parotid volume reduction was predictive of saliva production during and after RT in patients with head-and-neck tumors.

The normal tissue complication probability model defines a parotid gland ‘complication’ as a salivary flow rate $<25\%$ of pre-RT flow at 12 months (6,8,11). In other studies, glands exposed to low to moderate irradiation doses exhibited gradual functional recuperation over the course of many years post-RT (7,10,12). We found that saliva production substantially recuperated during the 24 months following 30 Gy irradiation and that mean saliva production returned to the normal level of 2.4 g. To avoid the sequelae of xerostomia in patients treated with RT for head-and-neck tumors, we recommend that they be carefully followed for 2 years after treatment.

Although xerostomia is a subjective symptom, objective functional assessments are available (6–12). Salivary flow rate measurement, primarily used to assess parotid gland function, is an invasive technique. The Saxon test—a simple, low-cost technique—can objectively measure saliva production, a factor included in the diagnostic criteria for Sjögren’s syndrome (20,21). We recommend that patients undergoing RT for head-and-neck tumors be routinely checked with this test during and after treatment, although some patients with oral tumors, especially older individuals, may find it difficult to chew a gauze pad for 2 min.

Our longitudinal data demonstrated that saliva production and parotid volumes are at the nadir 2 weeks and 6 months after RT, respectively. This discrepancy may be attributable to radiation-induced inflammatory changes. At 2 weeks after RT, the presence of oral mucositis may make it difficult for patients to perform the Saxon test and saliva measurements may be lower than the actual saliva levels. In addition, at that time point, inflammatory changes may result in enlarged parotid volumes. Nonetheless, although we must consider the effects of surgical intervention on morphological and functional parotid gland changes, the longitudinal volume changes in the ipsi- and contralateral parotid glands of our patients were compatible. Under our preoperative chemo-RT protocol, we administered S-1, a novel oral fluorouracil derivative (22). To the best of our knowledge, there have been no reports suggestive of a relationship between S-1 and salivary dysfunction after the completion of treatment.

Our study entails some limitations. Although we evaluated only parotid glands, radiation fields should have included submandibular, sublingual and minor salivary glands. RT should also provide potential damages to other salivary glands. Furthermore, the ipsilateral submandibular gland in all patients except one was resected at the surgery. We cannot ignore the potential influences of surgical procedures on the Saxon test. However, total saliva is mainly produced by the parotid glands, and radiation injury to salivary glands primarily results from damage to the parotid glands (1,2). Our results must be validated by a large prospective study. Efforts are underway at our hospital to collect longitudinal data on parotid and submandibular volumes and on saliva production in patients treated with definitive RT including IMRT.

In conclusion, although parotid volumes and saliva production were decreased after 30 Gy irradiation, we observed the recuperation of morphological and functional changes in the course of a 2-year follow-up in patients treated for advanced oral cancer. Despite individual variations, a reduction in the parotid volume may be predictive of saliva production during and after RT in patients with head-and-neck tumors. To avoid the sequelae of xerostomia, these patients should receive oral care for at least 2 years after RT.

Acknowledgement
We thank Dr. Chitose Takada from Takada Chitose Clinic for technical help.
Conflict of interest statement

None declared.

References