Prevention of radiation-induced xerostomia by submandibular gland transfer

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ABSTRACT: *Background.* This study was carried out for the purpose of evaluating the efficacy of submandibular gland transfer to prevent radiation-induced xerostomia.

Methods. Thirty-eight patients with oropharyngeal carcinoma were recruited. Twenty-six submandibular glands were transferred into the submental space to elude radiotherapy in 24 patients (transfer group); the submandibular gland was not disturbed in the control group ($n = 14$). The salivary flow rate, xerostomia, and quality of life (QOL) were assessed preoperatively, postoperatively, and after radiotherapy. The swallowing function was then evaluated after radiotherapy.

Results. All the transferred glands survived and functioned after radiotherapy. The submandibular salivary flow rate recovered by 6 months after radiotherapy in the transfer group, whereas the flow rate declined drastically after radiotherapy and remained at a low level in the longer term in the control group. Two years after radiotherapy, 92.3% of patients in the transfer group had no or minimal xerostomia. QOL in the transfer group was better than that in the control group from 3 months after radiotherapy. Histologically, the majority of the transferred glands had normal glandular acini and ducts. There was no significant difference in dysphagia between the groups.

Conclusions. The submandibular gland can be successfully transferred to the submental space, thus preserving salivary function and preventing radiation-induced xerostomia. The transfer of the submandibular gland can improve the QOL by alleviating xerostomia, although it did not relieve dysphagia in this study. © 2011 Wiley Periodicals, Inc. *Head Neck* **34:** 937–942, 2012

KEY WORDS: submandibular gland, xerostomia, radiotherapy, dysphagia, quality of life

Radiation is a primary or secondary therapeutic modality in most patients with head and neck cancer, resulting in salivary gland dysfunction in almost all patients. Xerostomia is the most common side effect of radiotherapy (RT) for head and neck cancer, occurring in up to 90% of patients who undergo this conventional treatment.[1] Xerostomia is a significant problem that causes impairment of mastication, deglutition, gustation, and phonation, increasing the risk of dental caries and oropharyngeal candidiasis. Ultimately, this can lead to decreased nutritional intake and weight loss. These all have a negative impact on the quality of life (QOL) of the patients.

Several preventative strategies are being explored to address the problem of radiation-induced xerostomia. Novel strategies, including the transfer of the submandibular gland,[2] the use of amifostine,[3] and intensity-modulated radiation treatment (IMRT) to spare the parotid and/or submandibular gland[4,5] have met with varying degrees of success.

Because the submandibular glands contribute 2 thirds of the resting production of saliva (approximately 200–300 mL/day/1 gland), it is feasible that xerostomia would be alleviated if the function of the submandibular gland was preserved by being surgically transferred to the submental space before RT. The purpose of this study was to evaluate the efficacy of submandibular gland transfer to prevent radiation-induced xerostomia.

PATIENTS AND METHODS

A total of 38 patients with head and neck cancer were enrolled from June 2002 to October 2007. The patients were divided in 2 groups: the patients in the transfer group were in the Fourth Ward and the patients in the control group were in the Third Ward in our hospital. Equal technical levels and clinical pathways existed in both of the 2 wards. The transfer group had 24 patients (22 men, 2 women). Ages ranged from 31 to 72 years, with a mean age of 56.0 years. The control group had 14 patients (10 men, 4 women; age range, 36–71 years; mean, 56.1 years). The primary sites and TNM classification of the carcinoma are shown in Table 1 and Table 2. The mean ($\pm$SD) duration of follow-up was 24.0 $\pm$ 17.1 months in the transfer group and 24.7 $\pm$ 14.5 months in the control group. There was no statistically significant difference between the 2 groups with regard to sex ($p = .56$), age ($p = .964$), primary site ($p = .501$), TNM classification ($p = .865$), and duration of follow-up ($p = .823$). All patients in the 2 groups had tumor resection, neck dissection, flap reconstruction if necessary, and RT

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TABLE 1. Demographic details of patients and tumor characteristics.

Factor	No. of patients (%)* Transfer group	Control group
Sex		
Male	22 (91.7)	10 (71.4)
Female	2 (8.3)	4 (28.6)
Age, y		
Median	56.0	56.1
Range	31–72	36–71
TNM classification		
T1N0M0	2 (8.3)	2 (14.3)
T1N1M0	0 (0)	2 (14.3)
T2N0M0	7 (29.2)	2 (14.3)
T2N1M0	3 (12.5)	1 (7.1)
T2N2M0	1 (4.2)	0 (0)
T3N0M0	3 (12.5)	0 (0)
T3N1M0	1 (4.2)	1 (7.1)
T4N0M0	2 (8.3)	2 (14.3)
T4N1M0	5 (20.8)	3 (21.4)
T4N2M0	0 (0)	1 (7.1)

*Except as otherwise noted.

bilaterally. Of the 24 patients, submandibular gland transfers were performed on the contralateral side to the primary tumor in 22 patients and bilaterally in 2 patients.

The research protocol was approved by the Peking University Institution Review Board, and all participants signed an informed consent document for submandibular gland function evaluation.

Seikaly and Jha method of submandibular gland transfer[2]

Submandibular gland transfers were performed in patients with clinically negative cervical lymph nodes. The facial artery and vein were ligated proximally and cut. Therefore, the gland was supplied via the retrograde flow through the distal facial vessels. The cut mylohyoid muscle allowed the repositioning of the submandibular duct and submandibular ganglion. The gland was then repositioned in the submental space with the distal facial vessels as a pedicle under the anterior belly of the digastric. Any suspicious nodes in the level I zone (submental and submandibular) were sent for frozen section biopsy. If these nodes were affected by cancer, the transfer was abandoned and a formal neck dissection was performed. The gland was anchored in place with absorbable sutures.

TABLE 2. Number of patients by primary site of the carcinoma.

Site	Transfer group	Control group
Hard palate	2	0
Gingiva	2	0
Tongue	1	3
Soft palate	6	3
Base of tongue	8	6
Oropharynx	4	2
Nasopharynx	1	0
Total	24	14

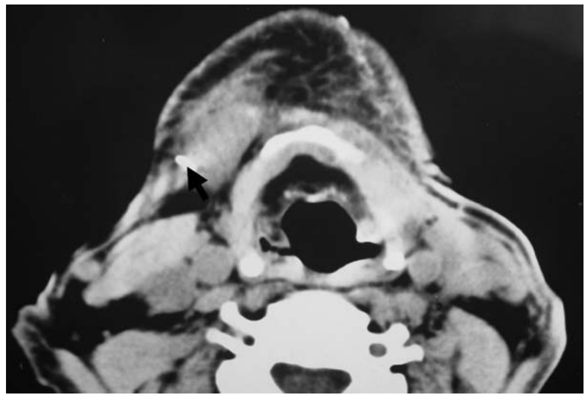

FIGURE 1. CT image after submandibular gland transfer. Note the high-density image in the posterior border of the gland.

The posterior and inferior borders were marked with titanium miniclips to help identify the gland during RT planning.

Radiation Treatment

RT was started within 1 to 2 months after surgery (including neck dissection in the affected side). The transferred gland was identified with the help of the titanium miniclips placed at surgery and confirmed by CT scans (Figure 1 and Figure 2). The gland was shielded. The total dose varied from 50 to 70 Gray (Gy) in the transfer group and 40 to 60 Gy in the control group in 1.8 to 2.0 Gy per fraction, treating once daily, 5 times a week, using conventional fraction. The mean dose was 50.92 Gy in the transfer group and 50.28 Gy in the control group; there was no significant difference between the 2 groups ($p = .161$).

Collection of saliva

Samples were collected in accord with a method introduced by Fox[6] at a standardized time of day (8–12 AM) because of diurnal variations in flow rates. Subjects refrained from eating and drinking for at least 60 minutes

FIGURE 2. Radiation field. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

before saliva collection. The orifices of Wharton's duct at the floor of the mouth were isolated with cotton rolls, and saliva was collected with a micropipette using gentle suction, whereas other oral secretions were blocked with cotton gauzes placed in the buccal and lingual vestibules (Supplemental Figure 1). Unstimulated samples were collected first, followed by the collection of the stimulated secretions by swabbing the 5% (w/v) citric acid on the dorsolateral surfaces of the tongue at 30-second intervals for 5 minutes, followed by evacuation of the accumulated saliva. The flow rate (*g*/5 min) was recorded. Measurements were made preoperatively, 1 and 2 weeks after surgery, and at 1, 3, 6, 12, 24, and 36 months after radiation treatment.

Assessment of xerostomia and QOL

QOL outcomes were evaluated using the University of Washington QOL questionnaire (Third Edition). This module contains 13 questions. All scales were rated on a 4-point Likert scale. All subscales were linearly converted to a 0–100 scale. Higher scores represent a greater QOL. Xerostomia were graded in accord with the scoring system designed by Wang Zhong-he, in which xerostomia was scored by 5 degrees (Supplemental Table 1). The patient was asked to circle the statements that best described his or her current status.

Evaluation of swallowing

The swallowing function was assessed in the patients with oropharyngeal carcinoma. Data were collected from 18 patients in the transfer group and 11 patients in the control group; all of these patients were male, the mean ages in each group were 58.3 and 56.8 years, respectively, and the mean dose of radiation was 48.55 and 50 Gy, respectively. There were no significant differences in these parameters between the 2 groups ($p = .828$, $p = .067$). The oropharyngeal defects were reconstructed with a forearm flap, except in 1 patient in the transfer group who received a lateral arm flap. The patients were examined at 12 months after RT with a fiberoptic endoscopic examination of swallowing (FEES).

The subjects were examined in the posture in which they normally ate. Initially, tongue movements and soft palate elevation were inspected. After appropriate topical anesthesia of the nasal cavity, a fiberoptic rhinolaryngoscope (model 11101 SP1; Karl Storz, Tuttlingen, Germany) attached to a color video monitor was inserted gently through the nasal floor. With the nasopharynx now visible, the subject was asked to dry swallow to allow the assessment of velopharyngeal competence. The scope was then deflected downward and passed into the oropharynx to a position that could show the whole laryngopharynx panoramically. The general appearance of the pharynx and larynx was noted. The adequacy of vocal cord movement was assessed during phonation and inspiration.

After completing the preswallowing assessment, we proceeded to a sequence of swallows of pudding and oral liquid dye. A spoonful of pudding (3 mL) was first administered, and the subject was instructed to hold the bolus in the mouth for 10 seconds. Any premature oral leakage to the pharynx or even preswallowing aspiration could be observed accurately by the endoscope. After moderate chewing, the subject was asked to swallow in a normal manner. Assessment was made on observation just before the initiation of swallowing and immediately after swallowing. Another bolus of 10 mL of diluted blue dye (methylthioninium chloride), water, and paste were then administered to subjects who safely passed the above-described examination. Procedures were terminated if any aspiration occurred. All observations were documented, including premature oral leakage, pharyngeal retention, and aspiration.

Histopathology

All lymph nodes in the level I zone (submental and submandibular) were sent for frozen section biopsy in the transfer group. A patient with submandibular gland transfer had tumor recurrence in the right side of the base of tongue at 12 months after transfer of the gland. The recurrent tumor was resected and the defect was reconstructed by free flap. During the operation, the transferred submandibular gland was removed, and this gland was collected for histologic examination.

Statistical analysis

Because the submandibular gland saliva flow rates were measured from the orifices of the ducts of both glands, the preoperative flow rate was halved to represent the output per gland in the 22 cases with contralateral submandibular gland transfer. For the post-RT measurements, the collected saliva was regarded to be produced by the transferred gland.

The submandibular gland saliva flow rates between the 2 groups were analyzed statistically using an independent-sample *t* test, whereas the flow rates among different times in both groups were compared using paired 2-tailed *t* tests. The xerostomia score and QOL score were analyzed using Mann–Whiney U test between the 2 groups and Wilcoxon signed-ranks test in each individual group. The relationship between xerostomia scores and QOL scores was analyzed using Pearson correlation analysis (SPSS for Windows software, version 13.0; SPSS, Chicago, IL).

RESULTS

All of the transferred glands were repositioned in the submental space outside the radiation fields and were assessed as functional by the collection of submandibular gland saliva. There was no injury to the marginal branch of the facial nerve due to submandibular gland transfer.

Of the 24 patients with submandibular gland transfers, 3 patients (12.5%) had experienced local recurrence, 2 patients (8.3%) developed a cervical lymph node metastasis in the transferred side, and 1 patient (4.2%) developed a second primary cancer of the larynx. None recurred in the submental space. One patient (7.1%) developed cervical lymph node metastasis and no patient had local recurrence in the control group.

Saliva examination

In the transfer group, the salivary flow rates at rest and after stimulation with 5% citric acid were reduced at 3

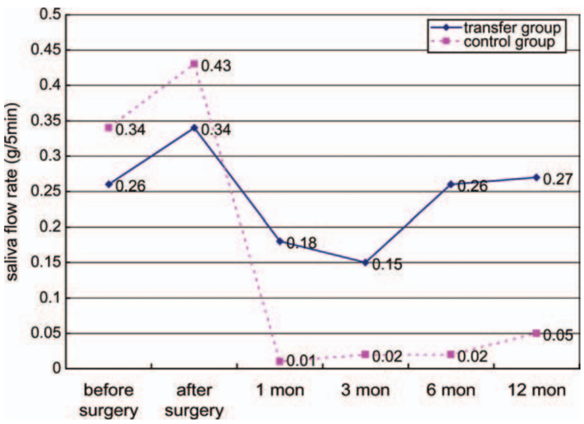

FIGURE 3. Unstimulated salivary flow rate. The difference between the 2 groups was statistically significant at 1 (p = .002), 3 (p = .006), 6 (p = .000), and 12 (p = .001) months after radiotherapy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

months after RT, and both recovered by 6 months after RT. In the control group, both the rest and stimulated submandibular salivary flow rate declined drastically after RT and remained at a low level in the longer term, as shown in Figure 3 and Figure 4.

The baseline salivary output of the submandibular glands (at rest and stimulated) showed statistically insignificant differences even after transfer, whereas a significant difference was found at every time interval following RT between the 2 groups. The postradiation salivary output showed no difference in the transfer group by 12 months after radiotherapy when contrasted with pre-RT, and there was a significant difference in the control group between pre- and post-RT at every time point.

Assessment of xerostomia

The incidence of severe xerostomia was 21% at 12 months after RT, and 7.7% at 24 months after RT in the transfer group. In the same group, 79% and 90% of patients had no or minimal levels of xerostomia at 1 year and 2 years after RT, respectively, compared with no improvement of xerostomia in the control group, even at 2 years after RT (Supplemental Table 2).

The saliva questionnaire data showed that there was a statistically significant difference between the 2 groups at 1 ($p < .000$), 3 ($p = .000$), 6 ($p = .006$), 12 ($p = .004$), and 24 ($p < .000$) months after the end of RT.

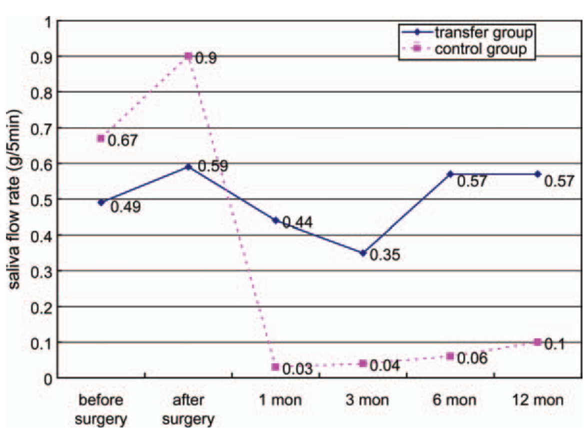

FIGURE 4. Stimulated salivary flow rate. The difference between the 2 groups was statistically significant at 1 (p = .002), 3 (p = .004), 6 (p = .000), and 12 (p = .000) months after radiotherapy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Swallow evaluation

All patients in the 2 groups had some degree of dysphagia, and the most common dysfunction of deglutition in these patients was pharyngeal retention (Supplemental Figure 2). There was no statistically significant difference between the 2 groups in dysphagia. No statistically significant difference was found between the 2 groups in swallow scores, as assessed by the University of Washington QOL questionnaire at 12 months after RT ($p = .797$).

QOL investigations

The QOL scores had a statistically significant difference between the 2 groups since 3 months after RT (Table 3). In the transfer group, the QOL scores had no statistically significant difference since 6 months after RT compared with the presurgical scores (Supplemental Table 3), whereas in the control group, the QOL scores at 24 months after RT had no statistically significant difference with the presurgical scores (Supplemental Table 4).

There was a linear correlation between the xerostomia scores and QOL scores in the patients with submandibular gland transfer at 24 months after radiotherapy (p = .002, $\gamma = 0.801$; Supplemental Figure 3).

All of the patients had impaired taste; the sensation of taste recovered in 78% of the transfer group patients at 6 months after RT compared with 64% of the control group patients at 12 months after RT.

Histopathology

All lymph nodes sent for frozen section biopsy in the transfer group were negative, which was proved by histologic examination (hematoxylin–eosin staining) after surgery.

Microscopically, the majority of the transferred gland showed normal glandular acini and ducts (Supplemental Figure 4A), whereas a small part of the gland showed extensive atrophy of the lobules (Supplemental Figure 4B). The atrophied lobules consisted of numerous

TABLE 3. QOL scores between the 2 groups.

Factor	Transfer group	Control group	p value*
Preoperative	155.0	98.0	.283
Postoperative, mo	146.0	107.0	.628
1	160.0	93.0	.159
3	173.0	80.0	.021
6	165.0	88.0	.038
12	175.5	75.5	.011
24	172.0	81.0	.025

Abbreviation: QOL, quality of living.
* Mann–Whitney U test; significant if $p < .05$.

intralobular ducts surrounded by layers of fibrous connective tissue that contained many capillaries and a diffuse inflammatory cell infiltration. The interlobular septa were expanded by dense, mature fibrous connective tissues.

DISCUSSION

The submandibular glands normally contribute 65% of the total volume of unstimulated saliva, whereas the parotid glands contribute 20% at rest but become the dominant gland during eating, contributing 50% of the salivary volume. Moreover, mucins produced by the submandibular glands, sublingual glands, and minor salivary glands are important to keep mucosa moist at all times.[7] Therefore, it is more important to protect the submandibular gland, which maintains the basal salivary production, than the parotid gland from RT-induced injury for patients who receive head and neck RT. It is reported that the tolerance dose values D_{50} for submandibular gland were 32.6 and 34.6 Gy at 6 and 12 months, respectively, after the completion of RT,[8] whereas Seikaly and Jha[9] reported that the transferred submandibular gland received between 8 and 14 Gy, which was only approximately a quarter to a third of the D_{50} values.

In theory, the function of the transferred submandibular gland could be preserved after RT, which has been confirmed by several clinical studies, including this present report.[2,9–11] There has been histological evidence to support this finding that the majority of the transferred gland showed normal glandular acini and ducts in 1 case of this study. Our study showed that the salivary flow rate of the transferred submandibular gland reached the presurgical level within 6 months after RT.

Spiegel et al[12] advocated that involvement of the submandibular gland in head and neck carcinomas must be through extension from a locally involved lymph node or the primary tumor, because the submandibular gland has no intraparenchymal lymph nodes. It is oncologically sound to consider transfer of the contralateral submandibular gland for patients with head and neck cancer when level I lymph nodes are unlikely to be involved.

Obviously, it is inappropriate to transfer the submandibular gland for patients with the anterior part of oral cancer because the submandibular and submental spaces (level I) are the lymphatic drainage regions of oral cancer. Patients with nasopharyngeal, oropharyngeal, hypopharyngeal, and laryngeal carcinoma were eligible to make contralateral submandibular gland transfer. All level I lymph nodes (submental and submandibular) were sent for frozen section evaluation in this study. If these nodes involved metastases, the transfer was abandoned and a formal neck dissection was performed.

Seikaly et al[9] reported that 26 patients who had preservation of 1 submandibular gland through surgical transfer had no disease recurrences on the side of the transferred gland or in the submental space during the 2 years of follow-up, which agreed with the results of this study. The procedure appears to be oncologically sound and safe.

The indication for submandibular gland transfer was patients with squamous cell carcinoma of the posterior part of oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx with a contralateral N0 neck. The procedure was contraindicated in patients with squamous cell carcinoma of the anterior part of the oral cavity, patients with contralateral metastases to the lymph node in the level I region, patients with Sjögren syndrome or sialadenitis, or patients with head and neck irradiation.

In the group of transferred gland, 25% of patients had the symptom of severe mouth dryness at 3 months after RT, whereas it decreased to only about 10% patients at 2 years after RT as the function of transferred submandibular gland recovered. These results were in accord with the conclusion of Seikaly et al,[9] who showed that xerostomia was prevented in 83% of the patients with submandibular gland transfer. Furthermore, Jha[13] reported that submandibular gland transfer was superior to pilocarpine in the management of radiation-induced xerostomia.

The D_{50} tolerance dose values for the parotid gland and submandibular gland are approximately 26 and 30 Gy, respectively.[8] The mean cumulative radioactive dose was >50 Gy in the 2 groups, including the parotid gland and the contralateral submandibular gland. When the total dose approached 50 Gy, the submandibular gland salivary flow showed a rapid decline in the nontransferred patients, who experienced grade 3 xerostomia even at 3 years after RT. These findings showed a strong association between the degree of xerostomia and the submandibular gland salivary flow.

It has been suggested that the late effects of RT may impair QOL more severely than the cancer itself.[14] A survey of 65 patients who survived for >6 months after RT found that 91.8% of patients complained of a dry mouth, 75.4% experienced a change in taste, 63.1% had dysphagia, 50.8% had altered speech, 48.5% developed difficulty with wearing dentures, 43% had difficulty for chewing or eating, and 38.5% of dentate patients had increased levels of tooth decay. In addition, pain was a common symptom (58.4%), interfering with daily activities in 30.8%. More than half of the patients (58.3%) had mood complaints, and 60% found that their social activities were interfered with by their physical condition. Epstein et al[15] also found that the most common oral symptoms that affected QOL, such as xerostomia, change in taste, dysphagia, speech difficulties, and oral pain, did not return to pretreatment levels by 6 months after RT. QOL in patients with head and neck cancer who received RT is influenced strongly by xerostomia.

There is also evidence that reduction of xerostomia results in improved QOL. Lin et al[16] and Jabbari et al[17] reported that both xerostomia and QOL scores improved significantly over time after IMRT, but not after conventional RT.

In this study, the QOL scores of all patients decreased significantly after the initiation of RT, and improved at 3 months post-RT, before recovering to presurgical levels 6 months after the completion of RT in the transfer group ($p = .059$). However, the QOL scores in the control group recovered at 24 months after RT ($p = .092$). These results imply that the alleviation of dry mouth appeared to be beneficial in improving the QOL of patients earlier. The QOL scores of patients had no significant difference at 1 month after RT between the 2 groups, which indicates that the acute radioactive injury for oral health (eg, acute mucositis) cannot be stopped with the preservation of saliva by the transferred submandibular gland.

Dysphagia is a common complication for patients with head and neck cancers due to radiotherapy. Different views were present on the correlation between xerostomia and dysphagia. Logemann et al[18,19] indicated that xerostomia affected the sensory process and comfort of eating more than bolus transport. Xerostomia changed patients' perceptions of their swallowing ability and affected their diet choices that they preferred such foods as liquid, pudding, or soft masticated. Furthermore, Rieger et al[20] found that the patients with submandibular gland transfer had a shorter duration of oral containment and overswallowing sequence duration than the patients who did not undergo a gland transfer. They concluded that the maintenance volume of saliva may promote a more time-efficient swallowing behavior. In the present study, no significant difference was found between the 2 groups in dysphagia, including premature oral leakage, pharyngeal retention, and aspiration, also found in the study by Reiger et al.[20] The shorter duration of swallowing did not improve the quality of swallowing.

The most commonly observed dysfunction of swallowing in the 2 groups was pharyngeal retention (93.3% with pudding and 100% with paste), similar to the study by Wu et al[21] that demonstrated 93.5% of the nasopharyngeal carcinoma patients suffered pharyngeal retention after RT. We also found that multiple impairments of pharyngeal function were a feature of these patients after RT. The possible causes related to pharyngeal retention were poor pharyngeal constriction and failure of upper esophageal sphincter relaxation. We presume that the swallowing function disorders may be caused by radiation-induced injury to the oropharyngeal organs.

CONCLUSIONS

This study demonstrated that the submandibular gland could be successfully transferred to the contralateral submental space with the preservation of gland function. Gland transfer prevented radiation-induced xerostomia in 80% to 90% of the patients with head and neck cancer after RT. The alleviation of xerostomia may be beneficial to the improvement of the QOL of the patients. Submandibular gland transfer cannot relieve dysphagia in these patients, which may be caused by the radiation injury to the oropharyngeal organs.

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