Assessment of salivary gland dysfunction after radioiodine therapy for thyroid carcinoma using non-contrast enhanced CT: The significance of changes in volume and attenuation of the glands

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Purpose

To correlate the extent of salivary dysfunction assessed by salivary gland scintigraphy with changes in the volume and attenuation of salivary glands on non-enhanced CT in postoperative patients with thyroid cancer treated with radioiodine therapy.
Methods and Materials

1. Subjects

The protocol for this retrospective study was approved by our institutional review board without requirement of informed consent.

The study subjects consisted of 40 patients:
- 13 were male (age range, 21-80 years; mean age, 61 years)
- 27 were female (age range, 28-75 years; mean age, 55 years).

The subjects were collected from January 2006 to January 2011.

All the patients had undergone a total thyroidectomy for well differentiated thyroid carcinoma.

We divided the patients into 4 groups according to the number of received doses of RIT:
- 20, 10, 4 and 6 patients received 1, 2, 3 and 4 doses, respectively.

The individual doses ranged from 5.1 to 5.6 GBq (139 to 150 mCi), with a mean of 5.3 GBq (144.5 mCi). The right submandibular gland was resected in 4 patients and the left submandibular gland was resected in one patient. None of the patients received concomitant or induction chemotherapy, nor did they have Sjogren syndrome or any other diseases of the parotid or submandibular glands. None of the patients used any medication known to affect salivary gland function.

2. Imaging examinations

Salivary gland scintigraphy and non-contrast enhanced neck CT were performed before the initial RIT in all patients. The average time interval from pretreatment salivary gland scintigraphy and CT to the initial RIT was 8 days (range, 1-15 days). Changes in the salivary glands after RIT were evaluated on the scintigraphy and CT scans obtained with the average interval of 9 months (range, 6 to 12 months) since the last therapy. Scintigraphy and CT scans were performed on the same day for all patients.

Scintigraphy studies
The salivary gland function was estimated by salivary gland scintigraphy using 185 MBq (5mCi) Tc-99m pertechnetate. Fasting patients were studied in the supine position. Images were obtained using a dual head gamma camera (Millennium VG; General Electric Healthcare, Milwaukee, Wis) equipped with a low-energy, high-resolution collimator. Dynamic images (1 frame per minutes) were acquired for 30 minutes with a field of view including the head and neck. After 20 minutes, the salivary glands were stimulated with lemon juice given orally. Data were analyzed on a workstation (Entegra; General Electric Healthcare, Milwaukee, WI).

All salivary gland scintigraphic data were assessed by a radiologist. Depending on the salivary gland uptake and excretion, its function was classified into the following 4 grades:

- grade 1, normal uptake and excretion
- grade 2, mild dysfunction, decreased salivary uptake and delayed excretion, with oral activity equal to salivary uptake at 30-40 min
- grade 3, moderate dysfunction, markedly decreased salivary gland uptake and delayed excretion, with higher salivary gland activity than oral activity at 30-40 min
- grade 4, severe dysfunction, severely decreased salivary uptake and higher background than salivary activity during the entire study (9,10).

To judge the grade of function in the parotid and submandibular glands, we initially determined the grade of each side gland separately. For the final grade, we utilized the worse grade in cases with different grades of the bilateral glands, and the grade of the unilateral gland in cases with excision of the contralateral gland.

**CT studies**

CT examinations were performed using a 16-detector row scanner (Aquilion 16; Toshiba Medical Systems, Tokyo, Japan). CT images were obtained with the following parameters: the tube voltage, 120 kV; tube current, 280-400 mA (automatically adjusted for the patients' body build); gantry rotation time, 0.5 seconds; detector collimation, 1 mm; and a table feed of 12 mm per gantry rotation. Contiguous 3 mm thick slice axial images were reconstructed. All CT studies were performed without contrast enhancement.

All CT studies were assessed by a radiologist, who was blinded to the results of scintigraphy. The volume and attenuation of the bilateral parotid and submandibular glands were retrospectively measured in each patient on both CT images obtained before the initial RIT and after the last RIT. The volume of the salivary gland was measured by summation of products of an area of the salivary gland on each slice and slice thickness. The area of the salivary gland was obtained by manually contoured region of interest.
measurement. The percentage of volume reduction of each gland after treatment was calculated with the following formula:

\[
\frac{\text{pre-treatment volume} - \text{post-treatment volume}}{\text{pre-treatment volume}} \times 100.
\]

The attenuation of each gland was determined by a region of interest measurement (ROI size, 40-60mm²) on CT scans obtained before and after the RIT, and their difference

\[(\text{post-treatment attenuation} - \text{pre-treatment attenuation})\]

was defined as an attenuation change of the salivary gland. The mean of above mentioned percentage of volume reduction and attenuation change of the bilateral parotid and submandibular glands was used as a CT index for each salivary gland. The value of the unilateral salivary gland was utilized in cases with an excision of the contralateral gland.

3. Statistical analyses

All statistical analyses were performed using a commercially available software program (SPSS, version 15.0 for Windows; SPSS, Chicago, IL). The correlation between the grade of dysfunction of the gland on scintigraphy and the number of RIT sessions was assessed using Spearman's rank correlation test. The correlations of the volume reduction and attenuation change of the salivary glands with the dysfunction grade of the salivary gland on scintigraphy were assessed using a one-way analysis of variance. Multiple comparisons of volume reduction and attenuation changes of the group with each dysfunction grade were assessed using the Tukey honestly significant difference test. The comparison of the incidences between two groups was assessed using the \( \chi^2 \) test. \( \text{Ap value} < 0.05 \) was considered to be statistically significant. The cutoff value of the volume reduction percentage and attenuation change of the salivary gland to diagnose grade 4 (severe) dysfunction of the gland was determined by an ROC curve.
1. The grade of dysfunction on scintigraphy and its correlation with the treatment dose

The grade of function in the parotid gland in all patients before RIT was grade 1 in 32, grade 2 in 8, grade 3 in 0, and grade 4 in 0 patients, and that after RIT was grade 1 in 9, grade 2 in 4, grade 3 in 6, and grade 4 in 21 patients. The deterioration in the parotid gland function on scintigraphy increased with an increase in the number of radiation treatments ($r=0.593$, $p<0.001$, Spearman’s rank correlation test) (Table 1).

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**Table 1**

The grade of function in the submandibular gland in all patients before RIT was grade 1 in 31, grade 2 in 9, grade 3 in 0, and grade 4 in 0 patients, and that after RIT was grade 1 in 11, grade 2 in 12, grade 3 in 12, and grade 4 in 5 patients. The grade of dysfunction in the submandibular glands also increased with an increase in the number of treatments ($r=0.636$, $p<0.001$, Spearman’s rank correlation test) (Table 2).

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**Table 2**
When comparing the incidence of each grade of dysfunction after RIT in all patients, the parotid gland showed a significantly higher grade of dysfunction than the submandibular gland (p<0.002, chi-square test).

2. The results on CT and their correlation with the grade of dysfunction on scintigraphy

Due to the small number of total patients and to simplify the analysis, we combined grade 2 and 3 salivary dysfunction into one category and divided all of the patients into 3 groups depending on the results of scintigraphy; grade 1, grades 2 & 3, and grade 4 in the subsequent analyses.

**The volume reduction of the gland on CT vs the grade of dysfunction on scintigraphy**

The reduction volume (mean±standard deviation, 95% of confidence interval) in the parotid gland after RIT depending on the grade of scintigraphy was 2.5±4.2%, 0-5.8% for grade 1 (n=9); 7.9±5.2%, 4.2-11.7% for grades 2 & 3 (n=10); and 35.0±13.9%, 28.7-41.4% for grade 4 (n=21) (Figs. 1, 2).

The reduction volume in the parotid gland after the treatment significantly increased with an increase in the grade of dysfunction on scintigraphy (p<0.001, one way analysis of variance). A significant difference in the reduction volume was present between the grade 1 and grade 4 (p<0.001) and the grades 2 & 3 and grade 4 (p<0.001) groups, but not between the grade 1 and grades 2 & 3 groups, as determined by the Tukey honestly significant difference test (Fig. 3).

The reduction volume (mean±standard deviation, 95% of confidence interval) in the submandibular gland after RIT depending on the grade of scintigraphy was 4.0±3.1%, 2.0-6.1% for grade 1 (n=11); 14.7±9.2%, 10.8-18.5% for grades 2 & 3 (n=24); and 42.3±11.3%, 28.3-56.3% for grade 4 (n=5) (Figs. 4, 5).

The reduction volume in the submandibular gland after the treatment was significantly increased with an increase in the grade of dysfunction on scintigraphy (p<0.001, one way analysis of variance). There was a significant difference in the reduction volume between the grade 1 and grades 2 & 3 (p<0.001), grades 2 & 3 and grade 4 (p<0.001), and grade 1 and grade 4 (p<0.001) groups, as determined by the Tukey honestly significant difference test (Fig. 3).

**The attenuation change in the gland on CT vs the grade of dysfunction on scintigraphy**
The attenuation change (mean±standard deviation, 95% of confidence interval) in the parotid gland after RIT depending on the grade of scintigraphy was 4.3±3.7HU, 1.5-7.2HU for grade 1 (n=9); 4.3±3.4HU, 1.8-6.8HU for grades 2 & 3 (n=10); and 23.9±17.7HU, 15.8-31.9HU for grade 4 (n=21) (Figs. 1, 2).

The attenuation change in the parotid gland after the treatment significantly increased with an increase in the grade of dysfunction on scintigraphy (p<0.001, one way analysis of variance). A significant difference in the attenuation change was present between the grade 1 and grade 4 (p<0.002), and between the grades 2 & 3 and grade 4 (p<0.001) groups, but not between the grade 1 and grades 2 & 3 groups, as determined by the Tukey honestly significant difference test (Fig. 6).

The attenuation change (mean±standard deviation, 95% of confidence interval) in the submandibular gland after RIT depending on the grade of scintigraphy was 4.4±3.5HU, 2.0-6.7HU for grade 1 (n=11); 5.3±5.9HU, 2.8-7.8HU for grades 2 & 3 (n=24); and 10.2±2.8HU, 6.8-13.7HU for grade 4 (n=5) (Figs. 4, 5).

In the submandibular glands, there was no significant correlation between the attenuation change and the grade of dysfunction on scintigraphy. No significant differences were noted among the attenuation changes for each group (Fig. 6).

3. ROC curves and cutoff values

We determined the cutoff values of volume reduction and attenuation changes to diagnose grade 4 dysfunction of the salivary glands using ROC curves in both the parotid and submandibular glands (Figs. 7 and 8).

The best cutoff value for the volume reduction to diagnose severe dysfunction was 19.5% in the parotid gland and 31.0% in the submandibular gland, and that in the attenuation change was 9.8HU in the parotid gland.
Fig. 1: A 73-year-old female who underwent 2 radioiodine treatments showed mild dysfunction of the parotid gland on scintigraphy. Non-contrast-enhanced CT images (a) before and (b) after the treatment. Bilateral parotid glands showed only mild shrinkage (volume reduction of 12%) and an increase in attenuation (6HU) on the CT obtained after the treatment.

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Fig. 2: A 71-year-old female who underwent 3 radioiodine treatments showed severe dysfunction of the parotid gland on scintigraphy. Non-contrast-enhanced CT images (a) before and (b) after the treatment. The bilateral parotid glands showed prominent volume reduction (of 53%) and an increase in attenuation of 32HU on CT after the treatment.

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Fig. 3: The volume reduction of the parotid and submandibular glands on CT after radiiodine therapy in relation to the dysfunction grade on scintigraphy (Tukey honestly significant difference test). In the parotid gland, a significant difference in the volume reduction was present between the following groups: grade 1 and grade 4 (p...
**Fig. 4:** A 46-year-old female who underwent 2 radioiodine treatments showed mild dysfunction of the submandibular gland on scintigraphy. Non-contrast-enhanced CT images (a) before and (b) after the treatment. The bilateral submandibular glands showed a mild volume reduction of 11% and an increase in attenuation of 12HU on CT after the treatment.

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Fig. 5: A 68-year-old female who underwent 4 radioiodine treatments showed severe dysfunction of the submandibular gland on scintigraphy. Non-contrast-enhanced CT images (a) before and (b) after the treatment. The bilateral submandibular glands showed prominent volume reduction of 56%, but a minimal increase in attenuation of 14HU on CT after the treatment.

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**Fig. 6:** The attenuation change of the parotid and submandibular glands on CT after radiiodine therapy depending on the dysfunction grade on scintigraphy (Tukey honestly significant difference test). In the parotid gland, a significant difference in the attenuation increase was present between the following groups: grade 1 and grade 4 (p

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**Fig. 7**: The ROC curves of the volume reduction % and attenuation change to diagnose severe dysfunction of the parotid gland.

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Fig. 8: The ROC curves of volume reduction % and attenuation change to diagnose severe dysfunction of the submandibular gland.

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Conclusion

In conclusion, a reduction in volume of the parotid and submandibular glands and an increase in attenuation in the parotid gland on non-contrast enhanced CT can be indicators of the grade of salivary dysfunction in patients who have undergone postoperative RIT for thyroid carcinomas.
References


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