ORIGINAL ARTICLE

LATE SIDE EFFECTS OF RADIOACTIVE IODINE ON SALIVARY GLAND FUNCTION IN PATIENTS WITH THYROID CANCER

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Abstract: *Background.* The purpose of this study was to assess the late side effects of radioiodine therapy (RIT) on salivary gland function. One hundred eighty two patients were evaluated.

Methods. Assessment of salivary gland function was performed with salivary gland scintigraphy (SGS), sialometry, and subjective open questions to determine common side effects of RIT on salivary gland function.

Results. RIT had a strong association with decreased elimination counts by SGS. Patient age was the only variable associated with sialometry; age and the use of xerostomic drugs were strongly associated with decreased mean values of salivary flow. Dysphagia was strongly associated with RIT. Using multiple logistic regression analysis, age was determined to be an important factor associated with salivary gland dysfunction, and RIT was associated with impairment of saliva excretion.

Conclusion. These results show that patients subjected to RIT have more difficulty in draining saliva, mainly from the parotid glands, which is associated with clinical dysphagia in this subset of patients. © 2010 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2010

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Saliva has several significant roles in maintaining oral function through the action of proteins such as amylase, immunoglobulins, and lysozymes. It also lubricates the oral mucosa, which allows for proper speaking, swallowing, and tasting. Loss or decrease in salivary production or flow can impair the ability to perform these functions and is remarkably associated with postradiation or radioiodine treatment morbidity.[1] In the unstimulated state, about two-thirds of the normal volume of saliva is produced by submandibular glands. However, depending on the type of stimuli, the parotid glands can account for about 50% of the saliva volume.[2]

According to Helman et al,[3] salivary glands concentrate iodine by substituting it for Cl^- as a substrate in the $Na^+/K^+/Cl^-$ co-transport system. This ability to concentrate iodine and radioactive iodine makes the salivary glands potential targets during and after the diagnostic or therapeutic use of these substances.[1,4] As a

consequence, sialadenitis, taste disturbances, xerostomia, and an increase in the number of dental cavities are recognized as short-term and long-term effects of radioiodine therapy (RIT) on salivary glands.[1]

The purpose of this study was to describe the late side effects of RIT associated with salivary gland function in patients treated for differentiated thyroid carcinoma who have all received a total thyroidectomy followed by adjuvant therapeutic doses of radioactive iodine in selected patients.

MATERIALS AND METHODS

Design. A cross-sectional study of patients with differentiated thyroid cancer who have undergone total thyroidectomy accompanied by adjuvant RIT in selected patients from 1997 to 2006 was performed. Patients subjected to prior head and neck radiation or with symptoms of sicca syndrome were excluded. The study was approved by the institutional ethics committee (number 762/06), and all patients signed the approved informed consent form.

Patients were invited to participate in this study as part of their follow-up medical consultations. All the patients were taking suppressive doses of levothyroxine and had normal thyroid hormone levels. Only patients from 2 months to 10 years from treatment end were included, with a median posttreatment time of 24.0 months. The independent variables were age, sex, radioiodine dose, use of xerostomic drugs, and complaints of xerostomia and dysphagia. The dependent variables were the uptake and elimination percentage from salivary gland scintigraphy (SGS) and the unstimulated and stimulated salivary flow from sialometry.

Data regarding xerostomic drug use were obtained by asking each patient if he or she used any antidepressant, antihistaminic, or hypotensive drugs.

Measures. Patients were categorized by age ($\leq$45 years or $>$45 years) and RIT dose ($<$150 mCi or $\geq$150 mCi). The following subjective open questions were asked to all patients:

Dry mouth: "Do you feel your mouth is dry?"
"For which periods of the day?"

Swallowing: "Do you have difficulty eating?"
"What kind of foods?"

Speaking: "Do you have any difficulty speaking?"

Tasting: "Do you have any taste disturbances?"
"What flavors?"

Salivary glands: "Do you have any swelling in the salivary gland regions?"
"When does it occur?"

Salivary Gland Scintigraphy. SGS was performed with a gamma camera (GE StarCam 4000, GE Medical Systems, Milwaukee, WI) fitted with a low-energy high-resolution collimator; the energy peak was set at 140 KeV with a 15% window. Each patient received 10 mCi (370 MBq) of $^{99m}TcO_4^-$ intravenously. Dynamic images were obtained in 90 seconds (1 second per image) with a 128 $\times$ 128 matrix with anterior projection. Static images of anterior and lateral projections, with a 256 $\times$ 256 matrix, were obtained with 180 seconds per image, before and after salivary gland stimulation with 500 mg ascorbic acid (Cewin, Sanofi-Synthelabo, São Paolo, Brazil) orally administer for 5 minutes. At the workstation computer, regions of interest were created on the salivary gland regions, and the regional counts were verified. The uptake rate was calculated for each major salivary gland (bilateral parotid and bilateral submandibular) as the count percentage of the real dose that was retained in each pair of glands. The real dose was 10 mCi after subtracting the counts retained in the local injection site and the counts that remained in the syringe. The elimination fraction was calculated as the difference between the count in each pair of glands pre-stimulus and post-stimulus. This difference was converted to a percentage of the total uptake. SGS was used to evaluate the salivary gland function as indicated by the percentage of $^{99m}TcO_4^-$ uptake and elimination.

Sialometry. Sialometry was performed as described by Koseki et al.[5] In brief, whole saliva was collected in a 15-mL tube for 5 minutes and 500 mg ascorbic acid (Cewin, Sanofi-Synthelabo) that was orally administer was used to obtain the stimulated salivary flow. The salivary flow rate was expressed in mL/minute. Normal parameters were based on data published by Jensen et al,[2] with cutoffs of unstimulated and stimulated salivary flow rates of 0.3 mL/minute and 1.5 mL/minute, respectively.

Statistical Analysis. For statistical analysis, the *t* test was used for univariate analysis, and multivariate analysis by multiple linear regressions was used to determine the independent variables that affected the sialometry and scintigraphy values. For comparisons, a p value $< .05$ was considered significant.

RESULTS

Four hundred patients that fulfilled the inclusion criteria were invited to participate in this study. Of those, 182 patients agreed to participate; 168 patients completed SGS, and 179 patients underwent sialometry. A total of 159 (87.5%) were women and 23 (12.6%) were men. The mean age was 49.7 years and the median age was 49 years (range, 23–89 years). All of the patients had received a total thyroidectomy; 177 patients had papillary carcinoma and 5 patients had follicular carcinoma. RIT was administered to 106 patients (58.2%), and the median dose was 135 mCi (range, 30–450 mCi); 82 patients received doses up to 150 mCi, and 26 patients received doses higher than 150 mCi. The reported occasional or continuous use of xerostomic drugs was reported in 79 patients (43.4%) and 17 patients (9.5%) were reported to have dry mouth and/or dysphagia (Table 1).

With respect to late side effects of radioiodine therapy, 5 patients (2.8%) were reported to have recurrent swelling of the salivary glands after RIT with or without pain. From these 5 patients, 3 had swelling of the salivary glands only while eating and it occurred spontaneously in the other 2 patients. Most patients that reported recurrent sialadenitis were unable to give precise information on the temporal relationship with radioiodine therapy. Sialadenitis was clinically diagnosed by a swelling in the region of major salivary glands with or without pain with spontaneous resolution and without clinical signs of bacterial or viral infection. Persistent taste disturbance was reported in 28 patients (15.6%) and 19 of those patients (67.8%) had been subjected to radioiodine therapy.

Univariate Analysis. For univariate analysis, RIT was evaluated as a possible variable that influences salivary gland function. For SGS, the uptake phase of RIT was not associated with a decreased uptake by salivary glands ($p = .81$). However, the patient's sex showed an association with the uptake phase by SGS. Men had decreased uptake in all major salivary glands (parotid glands $p = .05$; submandibular glands $p = .02$; and all salivary glands $p = .03$) as compared to women. Other variables did not show an association with salivary gland function.

Table 1. Descriptive analyses of dependent variables.

	Total no. of patients	No. of patients	%
Age	182		
≤45 y		72	40
>45 y		110	60
Sex	182		
Male		23	13
Female		159	87
RIT	182		
Yes		106	58
No		76	42
Xerostomic drugs	182		
Yes		79	43
No		103	57
Xerostomia	179		
Yes		162	90
No		17	10
Dysphagia	179		
Yes		162	90
No		17	10

Abbreviations: RIT, radioiodine therapy.

With respect to the elimination phase by SGS, only RIT had a strong association with decreased excretion ability in parotid glands, and this impairment was apparent when elimination was calculated for all glands together (parotid glands $p < .001$; all salivary glands $p = .002$). When doses of radioiodine were analyzed, there was no influence of doses higher or lower than 150 mCi in the uptake or elimination ability of salivary glands (Table 2).

For sialometry, age was the only variable associated with unstimulated salivary flow. Patients up to 45 years old had a mean value of unstimulated salivary flow that was higher than in patients over 45 years old ($p = .02$). Other variables did not show an association with unstimulated salivary flow rates. For stimulated salivary flow, age and the use of xerostomic drugs were statistically associated with decreased mean values of salivary flow rates ($p < .001$ and $p = .001$, respectively). In contrast to data from SGS, RIT was not associated with an altered stimulated salivary flow rate (Table 3).

Using univariate analysis, the association of RIT with xerostomia and dysphagia was

Table 2. Univariate analysis associating salivary gland scintigraphy results with dependent variables.

	% Parotid uptake*	% Submandibular uptake*	% Total uptake*	% Parotid elimination*	% Submandibular elimination*	% Total elimination*
Age						
≤45 y	1.48	1.67	3.14	29.37	27.74	28.91
>45 y	1.32	1.59	2.90	28.43	29.37	29.52
p value	.18	.51	.30	.63	.23	.66
Sex						
Male	1.08	1.25	2.33	28.76	27.20	28.27
Female	1.42	1.67	3.09	28.80	28.93	29.42
p value	.05	.02	.03	.99	.40	.58
RIT						
Yes	1.36	1.66	3.02	24.76	27.97	27.37
No	1.40	1.56	2.96	33.52	29.66	31.76
p value	.76	.44	.81	< .001	.22	.002
RIT						
≤150 mCi	1.41	1.70	3.11	26.14	28.75	28.24
>150 mCi	1.20	1.51	2.71	22.44	25.46	24.65
p value	.36	.42	.38	.28	.12	.11
Xerostomic drugs						
Yes	1.36	1.63	2.99	27.61	28.61	28.75
No	1.39	1.61	3.00	29.77	28.83	29.72
p value	.76	.91	.92	.27	.87	.48
Xerostomia						
Yes	1.47	1.70	3.17	29.88	28.70	29.63
No	1.36	1.61	2.97	28.56	28.75	29.20
p value	.59	.65	.61	.69	.98	.85
Dysphagia						
Yes	1.25	1.55	2.80	24.00	28.58	27.10
No	1.38	1.62	3.00	29.18	28.76	29.47
p value	.49	.71	.59	.12	.93	.30

Abbreviations: RIT, radioiodine therapy.
**Mean values.*

assessed. RIT and xerostomia were not associated ($p = .63$). A total of 11 patients who had xerostomia had previously undergone RIT and 6 patients had not. For dysphagia, this association was statistically significant ($p = .002$). Of the 17 patients that had dysphagia, 16 had undergone radioiodine therapy.

Multivariate Analysis. Variables with p values $\leq .25$ were included in the multivariate analysis. RIT interfered with the excretion ability of salivary glands, mainly in parotid glands, which was verified by the elimination phase and stimulated salivary flow by SGS and sialometry, respectively.

Age was the strongest predictor of parotid gland dysfunction; patient age affected both the uptake and elimination phases of parotid glands by SGS and unstimulated salivary flow rate and stimulated salivary flow rate by sialometry. The patient's sex also affected the uptake phase by SGS, and the use of xerostomic drugs affected the stimulated salivary flow rate by sialometry (Table 4).

DISCUSSION

In this study, incidences of sialadenitis and taste disturbance in patients with thyroid cancer were small as compared to those published by Alexander et al.[6] Our sialadenitis rate was 2.8%, and 15.6% of patients reported taste disturbances, while Alexander et al[6] published an incidence of 33% and 27%, respectively. These differences may be explained based on the design of the studies. The data published by Alexander et al[6] were collected in a prospective cohort-type study, which is more sensitive when subjective data are collected. In our study, which is a retrospective cohort-type, we depended on the memory of the patients and how important those side effects were to them.

As previously reported in other studies,[4,6,7] salivary glands become dysfunctional when

Table 3. Univariate analysis associating sialometry results with independent variables.

	USSF*	SSF*
Age		
≤45 y	.54	2.72
>45 y	.40	2.08
p value	.02	< .0001
Sex		
Male	.55	2.51
Female	.44	2.31
p value	.20	.36
RIT		
Yes	.42	2.23
No	.50	2.47
p value	.17	.10
RIT		
≤150 mCi	.42	2.29
>150 mCi	.41	2.01
p value	.87	.25
Xerostomic drugs		
Yes	.40	2.07
No	.49	2.53
p value	.12	.001
Xerostomia		
Yes	.33	2.36
No	.46	2.32
p value	.17	.84
Dysphagia		
Yes	.32	2.00
No	.47	2.35
p value	.15	.16

Abbreviations: USSF, unstimulated salivary flow; SSF, stimulated salivary flow; RIT, radioiodine therapy.
**Mean values.*

exposed to radioiodine. Many studies have demonstrated that radioactive iodine effects are dose-dependent,[6] and a recent study by our group showed that doses higher than 150 mCi have more side effects on salivary glands.[8] The ability of the salivary gland to eliminate $^{99m}TcO^{4-}$ after RIT diminishes significantly. The crossing of radioiodine through the $Na^+/K^+/Cl^-$ co-transport system depends on the ability of the transport system to correctly function; the function of this system is known to be affected by radiation during the radioiodine therapy.[3,9] Because this transport system is prevalent mostly in ductal cells,[10] excretion impairment can be associated with ductal system constriction, acute periductal inflammation, and chronic sclerosis induced by radioiodine. Consistent with this hypothesis, the results from our univariate and multivariate analysis showed impairment of the elimination phase, primarily in parotid glands, and of stimulated salivary flow rates by sialometry in patients that had received radioiodine therapy. There were no effects on the uptake phase by SGS, which can show $^{99m}TcO^{4-}$ in the periductal region, possibly because salivary gland damage related to radioactive iodine is more concentrated in the ductal system. Furthermore, periductal constriction makes saliva excretion more difficult when the production of saliva is higher, which is reflected by a diminished stimulated salivary flow rate.

The exploratory questionnaire used in this study was created to identify the most common complaints related to salivary gland dysfunction with no intention of developing a valid or reproducible questionnaire, but it was required because there is not a specific tool to describe oral effects of thyroid cancer treatment in the literature. Patient complaints of xerostomia is

Table 4. Multiple linear regression with independent variables.

	% Parotid uptake*	% Submandibular uptake*	% Total uptake*	% Parotid elimination*	% Submandibular elimination*	% Total elimination*	USSF*	SSF*
Age								
≤45 y	.045	.135	.056	.039	.837	.322	.010	<.001
>45 y								
Sex								
Male	.026	.016	.024	.825	.461	.717	.249	.528
Female								
RIT								
Yes	.817	.357	.719	<.001	.269	.002	.093	.036
No								
Xerostomic drugs								
Yes	.911	.764	.832	.575	.799	.650	.444	.028
No								

Abbreviations: USSF, unstimulated salivary flow; SSF, stimulated salivary flow; RIT, radioiodine therapy.
**p values.*

an important clinical finding that was expected to be associated with radioiodine therapy. However, in contrast to other studies,[2,6,7] it was not a significant side effect that was associated with this adjuvant therapy. These results may be a consequence of the study design that depends on the patient's ability to adapt and report about a new clinical status of saliva. On the other hand, dysphagia is a clinical finding that has been recently identified as a late side effect of radioiodine therapy.[8] Dysphagia is a well-recognized side effect of thyroid cancer treatment.[11,12] Recently, our group published new data about patients subjected to doses higher than 150 mCi; they had lower scores for swallowing and other functional domains that had a significant impact on their quality of life, as indicated by the University of Washington Quality of Life Questionnaire.[8]

The cutoff of 45 years old was used because it is used as an important prognostic reference value in patients with differentiated thyroid cancer.[13] As discussed in many studies,[14–16] age is an important factor that affects salivary gland function. This study reinforced the role of age on salivary gland function, with patients older than 45 years showing lower uptake and elimination counts by SGS and lower values of unstimulated salivary flow rates and stimulated salivary flow rates by sialometry.

In contrast to previous studies describing the influence of the patient's sex on salivary gland function,[15,17] which usually report that women have lower salivary gland function, our study showed lower uptake counts by SGS in men, but no other alteration in elimination counts or unstimulated and stimulated salivary flow rates that were associated with the patient's sex.

The patient's use of xerostomic drugs was associated with a lower stimulated salivary flow because the drugs likely alter the quantity of liquid in the saliva.[18]

It is important to understand that SGS and sialometry are different ways to verify salivary gland function and both focus on different phases of saliva production. SGS is able to detect the path by which some important ions are delivered into the duct system and can report on the overall composition of whole saliva with respect to water, proteins, and other ions. Sialometry is only able to quantify the volume of whole saliva, not the relative amounts of each component.

This study has some limitations because it is a retrospective cohort-type study. However, it confirms the effects of RIT on the patient's salivary gland function. The impairment of saliva excretion and dysphagia that are associated with RIT are the most important late side effects identified in this study. Impairment of saliva excretion can be reflected clinically as dysphagia and, as previously reported by our group,[8] it has a great impact on the quality of life of this subset of patients. Reports in the literature indicate that dysphagia is a surgical sequela and is not a late side effect of radioiodine therapy. However, results presented here indicate that prospective studies using videofluoroscopy exams may be important to verify different phases of swallowing and to clarify the impact of surgery and doses of RIT on the swallowing function.

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