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Original Article

Radiology Section

A Functional Scoring System Based on Salivary Gland Scintigraphy for Evaluating Salivary Gland Dysfunction Secondary to ^{131}I therapy in Patients with Differentiated Thyroid Carcinoma

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ABSTRACT

Introduction: Radioiodine therapy with ^{131}I (^{131}I therapy) after total or near-total thyroidectomy has been established as an effective treatment for Differentiated Thyroid Carcinoma (DTC), but can induce dry mouth symptoms by salivary gland damage and impair the patients' quality of life.

Aim: To propose a functional scoring system based on Salivary Gland Scintigraphy (SGS) findings that evaluates development of salivary gland dysfunction secondary to ^{131}I therapy in patients with DTC.

Materials and Methods: This retrospective study evaluated the records of 279 DTC patients who underwent SGS after one or more round(s) of ^{131}I therapy, using 370 MBqof ^{99m}Tc-pertechnetate. The SGS results were assessed using a novel functional scoring system in the Parotid Glands (PGs) and Submandibular Glands (SMGs) according to visual evaluations based on a three-point uptake score, Washout Rate (%WR) score after lemon-juice stimulation, and functional score. The scores were compared among pretreatment, low-dose (<10 GBq), and high-dose (>10 GBq) groups and among pretreatment, symptom-positive, and symptom-negative groups. Risk factors for dry mouth were analyzed by univariate and multivariate logistic regression analyses.

Results: Dry mouth symptoms developed in 15.4% of the DTC patients after ^{131}I therapy. The three-point uptake, %WR, and functional scores in both the PG and SMG were statistically significant between low-dose and high-dose groups, and between symptom-positive and symptom-negative groups. The PG/SMG functional scores were independent risk factors for dry mouth (odds ratio, 0.03 and 0.0007 respectively).

Conclusion: SGS-based PG and SMG functional scores were effective biomarkers to objectively evaluate salivary gland dysfunction, with the high strength of association with dry mouth symptoms.

Keywords: Dry mouth, Nuclear medicine imaging, Radioiodine treatment

INTRODUCTION

Radioiodine therapy with ^{131}I after total or near-total thyroidectomy has been established as an effective treatment for DTC [1]. Indeed, previous studies have reported significant reductions in the rates of disease recurrence and cause-specific mortality after ^{131}I therapy [2,3]. In general, ^{131}I therapy is a reasonably safe therapy, but a high cumulative dose is often associated with early and late-onset complications [4,5]. One of the most common chronic complications after ^{131}I therapy is salivary gland damage [4-10]. Both salivary glands and thyroid tissue have the sodium iodine symporter [5, 11-12], which results in a high concentration of ^{131}I in the salivary glands (about 30–40 times that in the plasma) [9, 11]. β-radiation from ^{131}I produces cytotoxic side effects in the salivary glands, and the incidence of chronic sialadenitis after ^{131}I therapy ranges from 11 to 43% [5,7,13].

The progression of chronic sialadenitis secondary to ^{131}I therapy leads to the symptoms of irreversible dry mouth and can impair the patients' quality of life for the long term. As characteristics of salivary gland damage after ^{131}I therapy, some articles have reported that the PG is more susceptible to ^{131}I-related damage than the SMG [14-16], and that SMG dysfunction is more associated with xerostomia than PG dysfunction [14]. Therefore, appropriate evaluations of salivary gland dysfunction are important.

Previous studies have explored the use of SGS and visual observation-based qualitative indices for evaluating parenchymal impairment in the salivary glands of patients who underwent ^{131}I therapy for DTC [14-18]. However, clinicians disagree on how to consolidate and interpret SGS findings and symptoms, as the existing qualitative indices are not predictive of patients' subjective symptoms of salivary gland dysfunction such as xerostomia. Further, these studies used relatively low cumulative doses (<10 GBq) of ^{131}I and did not separately assess the relative function of the PG and SMG. Therefore, the purpose of this study was to develop an objective functional scoring system based on SGS findings that better correlates with and predicts the development of salivary gland dysfunction secondary to ^{131}I therapy. Towards this end, we investigated multiple quantitative outcomes from the SGS of both the PG and SMG in a large population of patients with DTC after administering a varietyof different ^{131}I doses (3.7–5.5 GBq).

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Board of Kyushu University Hospital (Fukuoka, Japan) and written informed consent was obtained from all patients.

The data from 361 consecutive patients with DTC (96 men and 265 women) who underwent ^{131}I therapy at Kyushu University Hospital at least once between January 2011 and December 2015 were

retrospectively reviewed. Of the 361 patients, 314 patients (88 men and 226 women) who underwent SGS both before and after ^{131}I therapy were analyzed in this study. All patients had undergone near-total or total thyroidectomy before ^{131}I therapy and were histopathologically diagnosed with DTC. The inclusion criteria were as follows: (i) patients who underwent postoperative ^{131}I radioablation for thyroid remnant tissue, or (ii) patients who underwent ^{131}I therapy for metastatic or recurrent tumors from DTC. The exclusion criteria were as follows: (i) known history of salivary gland resection or external radiation therapy in the neck; (ii) baseline disease of salivary gland dysfunction before the initial ^{131}I therapy (e.g., sialadenitis including Sjogren's syndrome, sialolithiasis, or salivary gland tumor); (iii) usage of anticholonergic drugs and other drugs causing xerostomia; and (iv) suboptimal results or technical errors in SGS (e.g., incomplete immobility of the patients, inadequate injection technique). Consequently, 279 patients with DTC were included in this study. All 279 patients underwent SGS before initial ^{131}I therapy and after one or more round(s) of ^{131}I therapy. Additional ^{131}I therapy was repeatedly performed as long as posttreatment ^{131}I scintigraphy shows ^{131}I-avid uptake in residual tumors or metastasis based on American Thyroid Association (ATA) management guideline [19]. In these 279 patients, SGS was performed 12±1 months after the last ^{131}I therapy. All patients underwent thyroid hormone withdrawal for at least three weeks before ^{131}I therapy. A low-iodine diet was started two weeks before ^{131}I therapy. The per treatment ^{131}I dose ranged from 3.7 to 5.5 GBq. To prevent salivary gland damage, patients were instructed to suck on lemon candies during the first five days, beginning 1 day after ^{131}I therapy, in accordance with a previous report [20]. The patients' characteristics are shown in [Table/Fig-1].

Salivary Gland Scintigraphy

Imaging was performed using a hybrid camera combining a dual-head γ-camera with a spiral computed tomography scanner within the same gantry (Infinia; GE Health Care, Milwaukee, WI), which was equipped with a low-energy parallel-hole collimator. The patient was in a supine position, and the camera was positioned for an anterior head-and-neck projection. Dynamic imaging was performed with a 64 × 64 pixel matrix at five minutes per frame starting immediately after a bolus intravenous injection of 370 MBq (10 mCi) ^{99m}Tc-pertechnetate. Imaging continued for 40 minutes after injection. At 23 minutes after injection, we administered lemon-juice stimulation to the mouth of each patient, without inducing movement, while imaging was continued.

Analysis of Salivary Gland Scintigraphy findings

SGS imaging data were analyzed in several steps. First, saliva production was measured by assessing the degree of ^{99m}Tc-pertechnetate uptake in each salivary gland in the SGS images immediately before lemon-juice stimulation. A three-point uptake score was used to visually assess the degree of ^{99m}Tc-pertechnetate uptake in each salivary gland: 0–background; 1–decreased intensity; 2–normal intensity [Table/Fig-2]. Uptake scores of 0, 1, and 2 were respectively defined as intense dysfunction, no intense dysfunction, and no dysfunction in salivary glands, based on previous articles [15, 16]. The summed uptake score in the bilateral PG was defined as the PG uptake score and the summed uptake score in the bilateral SMG was defined as the SMG uptake score.

Second, saliva secretion was measured by the %WR. To do this, regions of interest were drawn on the dynamic images of the bilateral PG and SMG and time-activity curves were generated. The response of the salivary glands to lemon juice was noted on the time-activity curves as a sharp decline in the activity of the gland with a subsequent slow build up. Then, the %WR was calculated as follows [21]:

$$\%WR = (cmax - post\ counts)/cmax \times 100$$

where "cmax" is the prestimulatory maximum count value and "post counts" is the post-stimulatory minimum count value. Using this formula, the %WR in the PG (PG %WR) and the %WR in the SMG (SMG %WR) were respectively calculated. Decreased %WR was defined as a decrease in %WR more than 10% between before the initial therapy after the last therapy, according to the literature [15].

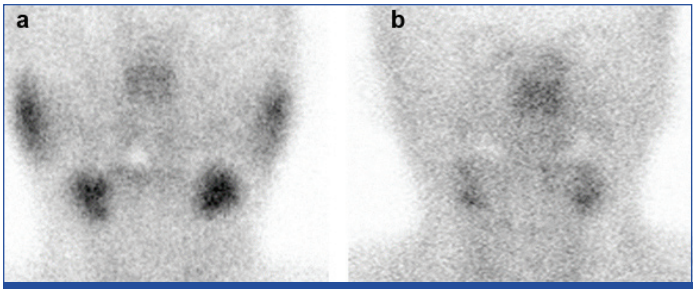
Third, the %WR was also assessed with a three-point %WR score based on the findings in the patients before initial ^{131}I therapy, as follows: 0, decreased %WR = 100%; 1, 10% < decreased %WR < 100%; 2, %WR ≤ 10%. The %WR scores of 0, 1, and 2 were considered to indicate intense dysfunction, no intense dysfunction, and no dysfunction in salivary glands, respectively. The summed %WR score in the bilateral PG was defined as the PG %WR score and the summed %WR score in the bilateral SMG was defined as the SMG %WR score.

Finally, the total scores for the PG and SMG, including the uptake scores and %WR scores, were defined as the PG functional score and the SMG functional score, respectively.

Based on the administrated cumulative ^{131}I dose, the 279 patients were categorized into the low-dose group (SGS following an^{131}I

Variables	Pretreatment group (n=279)	Low dose group (n=193)	High dose group (n=86)	Symptom-negative group (n=236)	Symptom-positive group (n=43)
Age (years)	16-75 (median:57)	18-75 (median:58)	16-73 (median:54)	18-75 (median:57)	16-75 (median:60)
Men/ Women	78/201	48/145	30/56	71/165	7/36
Papillary/ follicular/ papillary + follicular	258/18/3	186/4/3	72/14/0	219/14/3	39/4/0
TG level before ^{131}I therapy (ng/ml)	3.3-150000 (median:22)	3.3-7500 (median:11)	6.9-150000 (median 155)	3.3-150000 (median:17)	5.0-31000 (median:105)
Cumulative ^{131}I administered dose (GBq)	3.7-33.9 (median:4.5)	3.7-9.5 (median:4.0)	10-33.9 (median:13.6)	3.7-33.9 (median: 7.4)	7.6-33.7 (median:12.1)
TNM stage					
I	51 (18%)	38 (20%)	13 (15%)	48 (20%)	3 (7%)
II	21 (8%)	5 (3%)	16 (18%)	13 (5%)	8 (19%)
III	30 (11%)	26 (13%)	4 (5%)	27 (11%)	3 (7%)
IV A	101 (36%)	84 (43%)	17 (20%)	92 (40%)	9 (21%)
IV B	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IV C	76 (27%)	40 (21%)	36 (42%)	56 (24%)	20 (46%)
ATA risk classification					
Low	9 (3%)	8 (4%)	1 (1%)	8 (3%)	1 (2%)
Intermediate	170 (61%)	138 (72%)	32 (37%)	156 (66%)	14 (33%)
High	100 (36%)	47 (24%)	53 (62%)	72 (31%)	28 (65%)

[Table/Fig-1]: Baseline characteristics of the patients.



[Table/Fig-2]: Pattern of the three-point uptake scores, as observed by salivary gland scintigraphy. a): The uptake score in the bilateral parotid and submandibular glands is 2. b): The uptake score in the bilateral parotid glands is 0 and that of the bilateral submandibular glands is 1.

therapy dose of<10 GBq, n = 193), and high-dose group (SGS following an ^{131}I therapy dose of ≥10 GBq, n = 86). Additionally, the 279 patients were categorized into the, symptom-positive group (n = 43), and symptom-negative group (n = 236) based on the presence or absence of dry mouth symptom at the time of the SGS examination. The PG/SMG uptake scores, PG/SMG %WR scores, and PG/SMG functional scores were compared among pretreatment, low-dose, and high-dose groups, and among pretreatment, symptom-positive, and symptom-negative groups.

Analysis of association with dry mouth symptoms

Persistent subjective symptoms of dryness in the mouth and swallowing difficulty were judged as the presence of dry mouth symptom. The association between various clinical and radiological factors {age, sex, histological type, ATA risk classification, Thyroglobulin (TG) level before therapy (tumor marker), administered cumulative ^{131}I dose, and PG/SMG functional scores} and dry mouth symptoms were analyzed. The predictive value for dry mouth symptoms was also evaluated. Age, sex, and histological type were evaluated at the time of histopatho logical diagnosis as DTC. ATA risk classification was determined according to the guideline [19]. TG level was measured immediately before an^{131}I initial therapy under elevated thyroid-stimulating hormone levels.

STATISTICAL ANALYSIS

All statistical analyses were performed with the JMP® software package (version 8.0.2; SAS Institute, Cary, NC). Comparisons of the PG/SMG uptake score, PG/SMG %WR score, and PG/SMG functional score among pretreatment, low-dose, and high-dose groups and among pretreatment, symptom-positive, and symptom-negative groups were performed using Kruskal-Wallis tests and post-hoc pairwise tests.The correlations between clinical/radiological factors and dry mouth symptoms were analyzed by univariate and multivariate logistic regression analyses. Regression coefficients and odds ratios were calculated and 95% confidence intervals are given. The predictive value of dry mouth symptoms was determined using receiver operating characteristic curve analyses. Statistical significance for all tests was set at p< 0.05.

RESULTS

Clinical outcomes

Dry mouth symptoms developed in 43 of the 279 (15.4%) patients with DTC after ^{131}I therapy [Table/Fig-1]. Of these 43 patients, 10 were from the low-dose group (i.e., 5% of the low-dose group had dry mouth symptoms), and the other 33 were from the high-dose group (i.e., 38% of the high-dose group had dry mouth symptoms).

Comparisons among pretreatment, low-dose, and high-dose groups

The uptake scores, %WR scores, and functional scores in PG/SMG were significantly lower in the high-dose group than in the pretreatment and low-dose groups (p< 0.001 for all comparisons; [Table/Fig-3]). All three scores in PG were significantly lower in the low-dose group than in the pretreatment group (PG uptake score, p< 0.001; PG %WR score, p=0.002; PG functional score, p=0.001), although there were no significant differences between the pretreatment and low-dose groups in SMG [Table/Fig-3].

Comparisons among pretreatment, symptom-negative, and symptom-positive groups

The uptake scores, %WR scores, and functional scores in PG/SMG were significantly lower in the symptom-positive group than in the pretreatment and symptom-negative groups (p< 0.001 for all comparisons; [Table/Fig-4]). All three scores in PG were significantly lower in the symptom-negative group than in the pretreatment group (p< 0.001 for all comparisons), although there were no significant differences between the pretreatment and symptom-negative groups in SMG [Table/Fig-4].

Variables	Pretreatment group (n = 279)	Low-dose group (n = 193)	High-dose group (n = 86)
PG uptake score	4.0 ± 0	3.1 ± 1.2*	2.3± 1.5†
SMG uptake score	4.0 ± 0	3.9 ± 0.4	3.2 ± 1.1†
PG %WR score	4.0 ± 0	2.6 ± 1.5*	1.9 ± 1.8†
SMG %WR score	4.0 ± 0	3.9 ± 0.4	3.1 ± 1.2†
PG functional score	8.0 ± 0	5.7 ± 2.6*	4.2 ± 3.1†
SMG functional score	8.0 ± 0	7.8 ± 0.8	6.3 ± 2.2†

[Table/Fig-3]: Differences in the SGS parameters among pretreatment, low-dose, and high-dose groups.
SGS = salivary gland scintigraphy, PG = parotid gland, SMG = submandibular gland, %WR = washout rate.
*p< 0.05 vs. pretreatment group, Kruskal-Wallis tests and post hoc pairwise tests;
†p < 0.05 vs. low-dose group, Kruskal-Wallis tests and post hoc pairwise tests.

Variables	Pretreatment group (n = 279)	Symptom-negative group (n = 236)	Symptom-positive group (n = 43)
PG uptake score	4.0 ± 0	3.1 ± 1.2*	1.2 ± 1.0†
SMG uptake score	4.0 ± 0	4.0 ± 0.1	2.1 ± 0.9†
PG %WR score	4.0 ± 0	2.8 ± 1.5*	0.4 ± 0.9†
SMG %WR score	4.0 ± 0	4.0 ± 0.3	2.0 ± 1.0†
PG functional score	8.0 ± 0	5.9 ± 2.5*	1.5 ± 1.6†
SMG functional score	8.0 ± 0	7.9 ± 0.4	4.2 ± 1.7†

[Table/Fig-4] : Differences in the SGS parameters among pretreatment, symptom-negative, and symptom-positive groups.
SGS = salivary gland scintigraphy, PG = parotid gland, SMG = submandibular gland, %WR = washout rate.
*p< 0.05 vs. pretreatment group, Kruskal-Wallis tests and post hoc pairwise tests;
†p < 0.05 vs. low-dose group, Kruskal-Wallis tests and post hoc pairwise tests.

Relation factor analysis for dry mouth symptoms secondary to ^{131}I therapy

Univariate logistic analyses showed that ATA risk classification, TG level before therapy, cumulative ^{131}I dose, PG functional score, and SMG functional score were significantly associated with dry mouth symptoms. In the multivariate logistic analysis, only the PG functional score (χ^2 = 11.8, odds ratio = 0.03) and SMG functional score (χ^2 = 109, odds ratio = 0.0007) continued to show significant associations with dry mouth symptoms [Table/Fig-5].

Predictive analysis for dry mouth symptoms

Results of the receiver operating characteristic analyses to determine the predictive value of the ATA risk classification, TG level before therapy, cumulative dose of ^{131}I administered, PG functional score, and SMG functional score are shown in [Table/Fig-6]. Use of the optimal cut off thresholds for the SMG functional score differentiated the symptom-positive group from the symptom-negative group with the highest sensitivity, specificity, accuracy, and area under the curve [Table/Fig-6,7]. A significant difference was found between

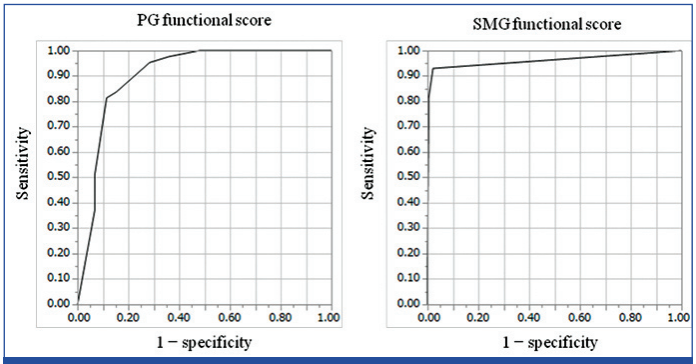
Characteristics		Univariate logistic analysis			Multivariate logistic analysis			
		$\chi 2$	Odds ratio	p	$\chi 2$	Odds ratio	95% CI	p
Age (years)	≥45 vs. <45	0.01	0.96	0.92				
Sex	Women vs. men	3.77	0.45	0.052				
Histological type	Papillary vs. follicular only	0.22	0.76	0.64				
ATA risk classification	High vs. low/ intermediate	18.1	0.24	<0.001	0.20	0.64	0.09–4.65	0.66
TG level before therapy (ng/mL)	≥230 vs. <230	12.0	0.28	0.0005	1.25	0.29	0.03–2.77	0.28
Cumulative ^{131}I dose (GBq)	≥5.1 vs. <5.1	44.7	0.07	<0.001	1.28	0.34	0.05–2.17	0.26
SGS findings								
PG functional score	≤1 vs. >1	45.5	0.07	<0.001	11.8	0.03	0.003–0.32	0.0006
SMG functional score	≤6 vs. >6	176	0.002	<0.001	109	0.0007	0.0001–0.008	<0.001

[Table/Fig-5]: Relation factor analyses for dry mouth symptoms.
CI = confidence interval, ATA = American Thyroid Association, TG = thyroglobulin, SGS = salivary gland scintigraphy, PG = parotid gland, SMG = submandibular gland.

the area under the curve obtained from the PG and SMG functional score (p=0.04).

Risk factor	Sensitivity	Specificity	Accuracy	AUC
High-risk ATA group	65% (28/43)	69% (164/236)	69% (192/279)	0.67
High pretreatment TG level (≥ 230 ng/mL)	44% (19/43)	83% (196/236)	77% (215/279)	0.66
High cumulative ^{131}I dose (≥ 5.1 GBq)	77% (33/43)	82% (193/236)	81% (226/279)	0.79
Low PG functional score (≤ 1)	81% (35/43)	89% (209/236)	87% (244/279)	0.90
Low SMG functional score (≤ 6)	93% (40/43)	98% (231/236)	97% (271/279)	0.96

[Table/Fig-6]: Predictive values of the risk factors for dry mouth symptoms.



[Table/Fig-7]: Predictive value of the Parotid (PG) and Submandibular Gland (SMG) functional scores for dry mouth symptoms secondary to ^{131}I therapy, as evaluated using receiver operating characteristic curve analyses. Receiver operating characteristic curves of the PG functional score (left) and SMG functional score (right) for predicting dry mouth symptoms are shown. The areas under the curve for the PG functional score and SMG functional score (0.90 and 0.96, respectively) were significantly different (p = 0.04).

DISCUSSION

The aim in this study was to develop an objective functional scoring system based on SGS findings that correlates with and predicts the development of salivary gland dysfunction secondary to ^{131}I therapy in DTC patients. We found significant differences in uptake, %WR, and functional scores in both PG and SMG among patients grouped by ^{131}I dose or dry mouth symptoms. PG dysfunction appeared to occur before SMG dysfunction after ^{131}I therapy. PG/SMG functional scores were shown to be independent risk factors for development of dry mouth symptoms.

In the present study, 15.4% of the patients with DTC (5% of the low-dose group and 38% of the high-dose group) developed dry mouth symptoms after ^{131}I therapy. Previous studies have shown that the incidence of xerostomia due to salivary gland dysfunction after ^{131}I therapy varies from 16 to 52% [10, 14-17], and this study showed the relative low incidence. These disparate results are likely related to differences in the cumulative administered dose of ^{131}I and follow up durations used in the various studies, but sucking on lemon candies after ^{131}I therapy in this study might affect the low incidence, as shown in previous reports [20].

All three SGS-based objective scores of salivary gland dysfunction (uptake scores, %WR scores, and functional scores) developed in this study were reduced after ^{131}I therapy, with the scores being the lowest in the high-dose group (generally, high-dose group < low-dose group < pretreatment group). Our results are in agreement with previous studies showing a positive correlation between the cumulative administrated ^{131}I dose and the degree of salivary gland dysfunction [14, 18]. It has been suggested that radiation injury in both the PG and SMG by ^{131}I therapy depends on the cumulative dose of ^{131}I. Goolden AW et al., [22] measured the salivary and plasma concentrations of ^{131}I, and estimated that the radiation dose to the salivary glands was approximately 7 Gy during the first 12 hours of therapy from doses of 3700–7400 MBq. Henriksson R et al., [23] reported that radiation exposure increases the amount of mast cell- and hyaluronic acid-mediated damage and the loss of serous acinar cells in the salivary glands, thereby reducing saliva production. Further, absorbed tissue doses between 7 Gy and 15 Gy could induce significant tissue inflammation and ductal obstruction, thus reducing salivary flow [24].

The SGS scores were also correlated with the presence of dry mouth symptoms. All three scores were reduced in both salivary glands when dry mouth symptoms were present (generally, symptom-positive group < symptom-negative group <pretreatment group). The degree of ^{99m}Tc-pertechnetate uptake in salivary glands indicates the capability of saliva production and %WR in SGS expresses saliva clearance from salivary glands to the oral cavity [21]. Sodium iodine symporters expressed on the surface of salivary gland cells incorporate iodine inside the cells and induce radiation exposure due to administered ^{131}I [25]. Also, the retention of radioiodine in the intralobular ducts of the salivary glands induces inflammation of the salivary gland duct wall and leads to poor saliva clearance due to narrowing of salivary gland ducts [5, 26]. Thus, poor saliva production and clearance associate with dry mouth symptoms and we think that the scoring system in the present study can concisely assess side effects in salivary glands after ^{131}I therapy. In addition, all three scores in PG were significantly reduced in symptom-negative group, compared with pretreatment group. The reduced scores that were observed in the symptom-negative patients suggest that SGS can detect salivary gland dysfunction by ^{131}I therapy before the development of symptoms. As salivary gland protection, amifostine has been reported to prevent salivary gland damage after administration of high ^{131}I dose [27]. Recently, sialoendoscopic intervention by dilating salivary ducts has also been reported as treatment for chronic sialadenitis [28, 29]. However, it

is difficult to obtain successful outcomes in total obstructive cases [28]. Early detection of salivary gland dysfunction by functional PG scores may contribute to determination of indication on such treatment for chronic sialadenitis.

In terms of the strength of the association and predictive value, the PG and SMG functional scores were independent risk factors for dry mouth symptoms and had the highest predictive value among the analyzed factors. As the uptake score reflects saliva production and the %WR score reflects salivary flow and secretion, we posit that the combined functional score better reflects the overall function of the salivary gland and therefore can be used as a feasible and simple method for evaluating salivary gland function secondary to ^{131}I therapy. On the other hand, the cumulative ^{131}I dose was not an independent risk factor for dry mouth symptoms. Some previous papers have reported that individual variations of ^{131}I uptake in salivary glands may influence the incidence of complication in PG [24, 30]. We speculate that individual differences of radiosensitivity in salivary glands as well as administered cumulative ^{131}I dose can associate with dry mouth symptoms.

Further, comparisons between the symptom-negative group and pretreatment group revealed different trends in the PG and SMG. All three scores in the PG were significantly reduced, but all three scores in the SMG were not significantly different between the symptom-negative and pretreatment groups. These results suggest that the PG is likely more sensitive to radiation than the SMG. The difference in radiosensitivity between the PG and SMG could be explained by the higher concentration of serous acinar cells in the PG [24] compared to the mucinous gland-rich SMG, because the serous cells have greater ability to concentrate iodine than mucous cells [5, 31]. Since SMG saliva production is not affected in symptom-negative patients and since the SMG produces nearly two thirds of the total saliva under the daily unstimulated state [27], dry mouth symptoms do not manifest despite PG dysfunction. These mechanisms could also explain the significantly higher predictive value of the SMG functional score compared to the PG functional score for dry mouth symptoms.

LIMITATION

Our study has several limitations. First, the SGS examination was performed approximately one year after the initial ^{131}I therapy. As salivary gland dysfunction is also known to manifest at later periods, the follow up duration in our study may not have completely captured all cases of salivary gland dysfunction. Second, we did not analyze the amount of saliva in the mouth as an objective measure of salivary gland dysfunction. Third, a decrease in %WR of >10% was defined as salivary gland dysfunction on SGS. We selected the cut off level of 10% according to previous articles [15], but we did not systemically investigate or validate whether the cut off level of 10% is the most optimal value. Finally, the present study is a retrospective study without consecutive cases and did not necessarily have a sufficient sample size for multivariate logistic regression analysis because of excluding DTC patients without undergoing SGS. Therefore, further studies are required to verify practical effectiveness of the functional scoring system.

CONCLUSION

This study showed that SGS could detect salivary gland dysfunction before the onset of symptoms. Dysfunction in the PG appears to occur before dysfunction in the SMG after ^{131}I therapy. Unlike the cumulative administered ^{131}I dose, the PG and SMG functional scores were independent risk factors for dry mouth symptoms, with the highest strength of association and predictive value.Therefore, we believe that clinicians should use the SGS-based PG and SMG functional scores as objective measures of salivary gland dysfunction secondary to ^{131}I therapy in patients with DTC for timely and efficient management of complications.

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