Value of Salivary Gland Scintigraphy after Initial ¹³¹ I Therapy for Differentiated Thyroid Carcinoma: Prediction of Salivary Gland Dysfunction after High Cumulative Dose ¹³¹I Administration

Yasuhiro Maruoka[1*], Shingo Baba[1], Takuro Isoda[1], Yoshiyuki Kitamura[1], Koichiro Abe[2], Masayuki Sasaki[3] and Hiroshi Honda[1]

[1]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[2]Department of Diagnostic Imaging and Nuclear Medicine, Tokyo Women's Medical University, Japan

[3]Department of Health Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[*]**Corresponding author:** Yasuhiro Maruoka, M.D, Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku Fukuoka-city, Fukuoka 812-8582, Japan, Tel: (81)-92-642-5695; E-mail: ymaruoka@radiol.med.kyushu-u.ac.jp

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Abstract

Objectives: Dry mouth symptoms induced by ¹³¹I therapy for differentiated thyroid carcinoma (DTC) can impair patients' quality of life over the long term. We investigated the value of early SGS findings in predicting the development of dry mouth symptoms in patients receiving high cumulative dose ¹³¹I therapy for DTC.

Materials and method: Eighty DTC patients who underwent SGS using 370 MBq of 99mTc-pertechnetate after the initial and second rounds of ¹³¹I therapy (cumulative ¹³¹I dose >10 GBq) between January 2010 and December 2013 were retrospectively analyzed. SGS was assessed using a 3-point uptake score and washout rate (%WR) after lemon-juice stimulation in the parotid (PG) and submandibular glands (SMG). Summed scores from bilateral PG and SMG were defined as the summed uptake score (SUS) and summed WR score (SWRS), respectively. Risk factors for dry mouth symptoms were analyzed by uni- and multivariate logistic regression analyses.

Results: SUS/SWRS after initial ¹³¹I therapy were significantly associated with dry mouth symptoms both in univariate analysis ($\chi 2$ and odds ratio: 39.5 and 0.03 for SUS, and 46.4 and 0.02 for SWRS, respectively) and in multivariate analysis ($\chi 2$ and odds ratio: 6.13 and 0.06 for SUS, and 8.40 and 0.04 for SWRS, respectively).

Conclusion: SGS after the initial ¹³¹I therapy can be a feasible biomarker for predicting development of dry mouth symptoms secondary to high-dose ¹³¹I therapy.

Introduction

Radioiodine therapy with ¹³¹I after total or near-total thyroidectomy is known to be an effective treatment for differentiated thyroid carcinoma (DTC) [1]. Several studies have reported a significant reduction in the rates of disease recurrence and cause-specific mortality in DTC patients after ¹³¹I therapy [2,3]. While ¹³¹I therapy is generally considered to be safe, a high cumulative dose has been reported to cause early- and late-onset complications in some cases [4,5]. Salivary gland damage is the most common long-term side-effect after high-dose ¹³¹I therapy [4-12]. As salivary glands and thyroid tissue possess the same sodium–iodine symporter molecule [4,13,14], ¹³¹I accumulates and reaches a high concentration (about 30–40 times of that in the plasma) in the salivary glands [13]. β-radiation from the accumulated ¹³¹I causes local cytotoxic side-effects, manifesting as salivary gland damage and chronic sialadenitis. Chronic sialadenitis affects 11%–43% of patients treated with ¹³¹I therapy [4,15,16] and presents with dry mouth or dysphagia. These symptoms of salivary gland dysfunction significantly impair patients' quality of life over the long term. Therefore, it is important that salivary gland dysfunction is quantitated objectively, and that patients at risk of development such symptoms are identified and treated early.

Previous studies have used salivary gland scintigraphy (SGS) for quantitative evaluation of parenchymal impairment of salivary glands in patients after ¹³¹I therapy for DTC. Bohuslavizki et al. have reported a progressive reduction in salivary gland function with the increase in the cumulative ¹³¹I

dose (15% after 0.4–0.6 GBq, 30% after 1.4–1.5 GBq, and up to 90% after 24 GBq ^{131}I) [17]. Caglar et al. [18] and Rasa et al. [19] have also reported a correlation between salivary gland dysfunction in SGS findings and the dose of ^{131}I administered, as well as subjective symptoms, such as xerostomia. However, SGS results are generally subjectively interpreted and objective measures based on SGS findings that can be used for quantitative assessment of salivary gland dysfunction are lacking.

A quantitative SGS-based marker of salivary gland dysfunction could potentially be used as a predictive biomarker of dry mouth symptoms arising from high-dose ^{131}I therapy. The purpose of this study was therefore to investigate the prediction of dry mouth symptoms after administration of a high cumulative ^{131}I dose, using SGS findings after the initial ^{131}I therapy for DTC.

Materials and Methods

Patients

This study was approved by our institutional review board and written informed consent from each patient was obtained. Data of 80 patients with DTC (29 men and 51 women) who underwent at least two rounds of ^{131}I therapy and had SGS after each round of ^{131}I therapy, between January 2010 and December 2013, were retrospectively analyzed (**Figure 1**). The patients ranged from 16–72-years-old (median: 53 years), and were histopathologically diagnosed with either papillary or follicular carcinoma. The inclusion criteria were as follows: (i) patients who underwent ^{131}I therapy for metastatic or recurrent DTC tumors; and (ii) patients who had a cumulative administered ^{131}I dose exceeding 10 GBq. The exclusion criteria were as follows: (i) known history of salivary gland resection; (ii) known history of external radiation therapy in the neck; (iii) baseline disease with salivary gland dysfunction before the first ^{131}I therapy (e.g., Sjogren's syndrome or salivary gland tumor); (iv) usage of anticholonergic drugs and other drugs causing xerostomia; and (v) suboptimal studies or technical errors in SGS (e.g., motion artifacts, inadequate injection technique).
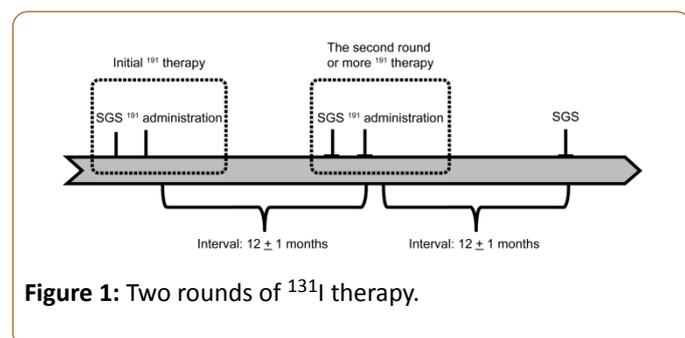

Figure 1: Two rounds of ^{131}I therapy.

All patients underwent thyroid hormone withdrawal for at least 3 weeks before ^{131}I therapy. A low-iodine diet was started 2 weeks before ^{131}I therapy. The ^{131}I dose ranged from 3.7 to 5.5 GBq, as per treatment dose. SGS was performed 12 ± 2 months after the initial and second round of therapy. The patient characteristics are shown in **Table 1**.

SGS

Imaging was performed using a hybrid camera combining a dual-head camera with spiral computed tomography (CT), using the same gantry (Infinia; GE Healthcare, Little Chalfont, UK) equipped with a low-energy parallel-hole collimator. The patient was placed in a supine position, and the camera was positioned for an anterior head-and-neck projection. Dynamic imaging was performed in a 64 × 64 pixel matrix, at 5 min per frame, starting immediately after a bolus intravenous injection of 370–444 MBq (10–12 mCi) 99mTc-pertechnetate. Imaging continued for 40 min after injection. At 23 min after injection, each patient was given lemon juice stimulation in the mouth, without moving, under continuous imaging.

Analysis of SGS findings

Table 1: Baseline characteristics of the patients.

Age (years)	16–72 (median: 53)
Men / women	29 / 51
Papillary / follicular	68 / 12
TG level before ^{131}I therapy (ng/mL)	7.9–54400 (median: 115)
Cumulative ^{131}I administered dose (GBq)	11.4–31.5 (median: 115)
TNM stage	
I	11 (14%)
II	16 (20%)
III	3 (4%)
IVA	17 (21%)
IVB	0 (0%)
C	33 (41%)
ATA risk classification	
Intermediate	31 (39%)
High	49 (61%)
TG = Thyroglobulin; ATA = American Thyroid Association	

SGS images taken immediately before lemon juice stimulation were used to assess the capacity for saliva production by the salivary glands. A 3-point uptake score was used to visualize the degree of 99mTc-pertechnetate uptake in each salivary gland (**Figure 2**) 0—decreased to background levels; 1—decreased, but more than background levels; 2—normal according to a previous article [20]. Scores of 0, 1 and 2 were respectively defined as non-function, dysfunction, and no dysfunction in each gland. The summed uptake score (SUS) derived by addition of the values from the bilateral parotid

glands (PGs) and submandibular glands (SMGs) was considered to represent the overall salivary production status.
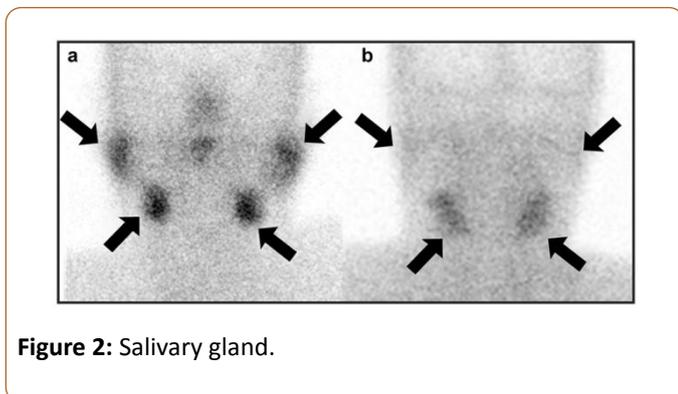

Figure 2: Salivary gland.

Next, the capacity for saliva secretion was measured by the washout rate, as follows. Regions of interest were drawn on the dynamic images of the bilateral PGs and SMGs, and time–activity curves were generated. The response of 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 buildup. The washout rate (%WR) was defined 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. According to the literature [19], decreased %WR was defined as a decrease in %WR more than 10% compared with %WR before the initial therapy.

Both the %WR in PGs (PG %WR) and %WR in SMGs (SMG %WR) were calculated. Finally, based on a previous study, the assessment of %WR was performed with a 3-point WR score, based on the findings in patients before ^{131}I therapy, as follows: 0: % decreased WR = 100%; 1: 10%: < decreased %WR < 100%; 2: %WR ≥ 10% [20]. %WR scores of 0, 1, 2 were respectively considered to indicate non-function, dysfunction, and no dysfunction in salivary glands. %WR score before the initial ^{131}I therapy was defined as 2 in all patients, based on that DTC patients before ^{131}I therapy in this study have no salivary gland dysfunction. The summed WR score (SWRS) derived by addition of the values of the bilateral PGs and bilateral SMGs was taken as representing the overall salivary secretion status. SUS, PG %WR, SMG %WR and SWRS between the positive-symptom and negative-symptom groups are presented in **Table 2**.

Table 2: The difference between symptom-negative group and symptom-positive group.

Histological type		
Papillary / follicular	42 / 7	26 / 5
TG level before 131I therapy (ng/mL)	2312 ± 9543	2644 ± 6823
Per treatment 131I administered dose	4.2 ± 0.5	4.3 ± 0.5
Cumulative 131I administered dose (GBq)	13.8 ± 5.8	14.2 ± 5.7
TNM stage		
I/ II / III / IVA / VB / VIC	10 / 9 / 2 / 11 / 17	1 / 7 / 1 / 6 / 16
Risk group		
Intermediate / high	23 / 26	23-Aug
131I scintigraphy findings in salivary glands after the first 131I therapy		
Positive / negative	Oct-39	15 / 16*
Salivary gland scintigraphy parameters		
SUS before the first 131I therapy	8 ± 0	8 ± 0
PG %WR before the first 131I therapy (%)	59 ± 8	60 ± 7
SMG %WR before the first 131I therapy (%)	55 ± 6	56 ± 5
SWRS before the first 131I therapy	8 ± 0	8 ± 0
SUS after the first 131I therapy	7.7 ± 0.7	6.0 ± 1.4*
PG %WR after the first 131I therapy (%)	56 ± 16	21 ± 21*
SMG %WR after the first 131I therapy (%)	52 ± 16	47 ± 11
SWRS after the first 131I therapy	7.5 ± 1.0	4.6 ± 1.7*
SUS after the second 131I therapy	7.1 ± 1.2	2.8 ± 1.4*
PG %WR after the second 131I therapy (%)	51 ± 22	5 ± 11*
SMG %WR after the second 131I therapy (%)	52 ± 8	32 ± 14*
SWRS after the second 131I therapy	6.8 ± 1.6	2.7 ± 1.7*
Δ SUS	0.6 ± 0.9	3.1 ± 1.5*
Δ SWRS	0.7 ± 1.2	1.9 ± 1.6*

SUS = Summed Uptake Score; SWRS = Summed Washout Rate Score; PG = Parotid Gland; SMG = Submandibular Gland *p<0.001 vs. symptom-negative group.

Finally, the differences in SUS and SWRS between the initial and second ^{131}I therapy sessions were defined as ΔSUS and ΔSWRS, respectively. Based on the presence or absence of dry mouth symptoms at the follow-up (at 12 ± 1 months after the last ^{131}I therapy), the 80 patients were categorized into a positive-symptom group (n = 31 patients) and a negative-

Type	Symptom-negative group (n = 49)	Symptom-positive group (n = 31)
Age (years old)	48 ± 14	53 ± 16
Men / women	26 / 23	3 / 28*

symptom group (n = 49 patients). SUS/SWRS and ΔSUS/ΔSWRS were compared between the positive-symptom and negative-symptom groups **(Table 2).**

Post-Therapy ^{131}I Scintigraphy

Post-therapy ^{131}I scintigraphy imaging was performed 5–7 days after ^{131}I administration andsingle-photon emission computed tomography;

Analysis of Post-Therapy ^{131}I scintigraphy findings

^{131}I scintigraphy images were used to visualize the degree of ^{131}I accumulation in the salivary glands, as a marker of the potential radiation exposure in salivary gland tissue. ^{131}I accumulation that exceeded background levels in at least either one of salivary gland was defined as positive, and ^{131}I accumulation equal to background levels in all salivary glands was defined as negative.

Statistical analysis

All statistical calculations were performed with JMP® package (version 13.0.0; SAS Institute). Comparisons of SUS/SWRS and ΔSUS/ΔSWRS between positive-symptom and negative-symptom groups were performed with the Mann–Whitney U test. Risk factors related to the development of dry mouth symptoms (salivary gland dysfunction) were analyzed by uni- and multivariate logistic regression analysis. Regression coefficients and odds ratios were calculated and 95% confidence intervals were determined. The predictive value of factors for dry mouth symptoms was analysed by receiver operating characteristic (ROC) curve *analysis*. Statistical significance for all tests was set at p<0.05.

Results

Comparison of SUS/SWRS and ΔSUS/ΔSWRS between the Positive- and Negative-Symptom Groups

In the overall study population, PG and SMG SUS were both (mean ± SD) 8 (0) before the initial ^{131}I therapy, and respectively 7.0 (1.4) (range: 2–8) and 6.4 (1.9) (range: 2–8) after the initial ^{131}I therapy, and 5.5 (2.5) (range: 0–8) and 5.2 (2.6) (range: 0–8) after the second round of ^{131}I therapy. Similarly, PG and SMG %WR were 64 ± 8% (49–86%) and 57 ± 6% (46–73%), respectively, before the initial ^{131}I therapy, 41 ± 25% (0–79%) and 50 ± 11% (20–74%) after the initial ^{131}I therapy, and 30 ± 27% (0–74%) and 44 ± 15% (0–65%) after the second round of ^{131}I therapy **(Table 2)**. Overall, 35 of 80 (43.7%) patients demonstrated decreased SUS and 38 of 80 (47.5%) patients had decreased SWRS after the initial ^{131}I therapy.

Additionally, 31 of 80 (38.8%) patients suffered dry mouth symptoms after the second round of ^{131}I therapy. SUS and SWRS were significantly less in the symptom-positive group

than in the symptom-negative group, after both the initial and the second ^{131}I therapy sessions (SUS: p<0.0001, SWRS: p<0.0001, at both instances). ΔSUS/ΔSWRS was significantly higher in the symptom-positive group than in the symptom-negative group (ΔSUS: p<0.0001, ΔSWRS: p=0.0003).

Risk factor analysis for dry mouth symptoms after ^{131}I Therapy

Univariate logistic analysis showed that sex, ^{131}I accumulation in salivary glands, SUS, and SWRS were significant association with dry mouth symptoms. After multivariate logistic analysis, only SUS and SWRS continued to show significant association with dry mouth symptoms (χ2 and odds ratio: 6.13 and 0.06 for SUS, and 8.40 and 0.04 for SWRS, respectively; **(Table 3)**.

Table 3: Risk factor analysis for dry mouth symptoms.

Characteristics		Univariate logistic analysis			Multivariate logistic analysis			
		χ2	Odds ratio	P	χ2	Odds ratio	95% CI	P
Age (years)	≥ 54 *vs.* < 54	3.21	0.44	0.07	0.02	0.81	0.03–11.1	0.88
Sex	Women *vs.* men	17.3	0.09	< 0.0001	0.98	0.34	0.04–2.96	0.32
Histological type	Papillary *vs.* follicular	0.05	0.87	0.82	1.83	0.12	0.004–2.51	0.18
TNM stage	/ *vs.* /	1.46	0.55	0.23	1.64	0.15	0.004–2.52	0.2
ATA risk group	High *vs.* intermediate	3.67	0.39	0.06	0.003	0.93	0.07–12.3	0.95
Recurrent disease	Positive vs. negative	0.31	0.73	0.58	0.24	0.59	0.06–4.85	0.63
TG level before therapy (ng/mL)	≥ 19 *vs.* < 19	0.43	0.71	0.51	0.35	0.46	0.03–6.70	0.56
Per treatment 131I dose (GBq)	≥ 4.1 *vs.* < 4.1	0.52	0.71	0.47	0.25	0.59	0.06–4.72	0.62
Cumulative 131I dose (GBq)	≥ 15.6 *vs.* < 15.6	1.57	0.55	0.21	2.65	0.09	0.003–1.61	0.1

131I accumulation in salivary glands	Positive vs. negative	6.84	0.27	0.009	1.65	0.28	0.03 – 1.92	0.2
SGS findings after initial 131I therapy								
SUS	≤ 7 vs. > 7	39.5	0.03	< 0.0001	6.31	0.06	0.003 – 0.55	0.01
SWRS	≤ 6 vs. > 6	46.4	0.02	< 0.0001	8.63	0.04	0.001 – 0.37	0.03

ATA: American Thyroid Association; TG = Thyroglobulin; SGS: Salivary Gland Scintigraphy; SUS: Summed Uptake Score; SWRS: Summed Washout Rate Score.

Predictive ability of SUS/SWRS for dry mouth symptoms

ROC curve analysis showed that symptom-positive and symptom-negative groups could be differentiated with 74% (23/31) sensitivity, 43% (21/49) specificity, 55% (44/80) accuracy, and an area under the curve (AUC) of 0.52, based on a cumulative ^{131}I dose with a cutoff threshold of 15.6 GBq. Positive or negative findings of ^{131}I accumulation in salivary glands differentiated symptom-positive and symptom-negative groups with 48% (15/31) sensitivity, 80% (39/49) specificity, 68% (54/80) accuracy. In comparison, SUS and SWRS, with a cutoff threshold of 7 and 6, differentiated between the two groups with 84% (26/31) and 90% (28/31) sensitivity, 82% (40/49) and 80% (39/49) specificity, 83% (66/80) and 84% (67/80) accuracy, and AUC of 0.85 and 0.90, respectively (**Figure 3**).
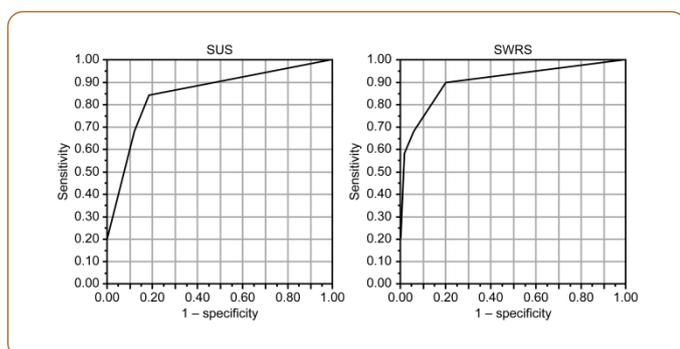

Figure 3: ROC curve.

Discussion

We addressed the utility of SGS findings after the initial ^{131}I therapy to assess the risk of dry mouth symptoms after high-dose ^{131}I therapy in patients with DTC. While SUS and SWRS progressively declined in all patients after ^{131}I therapy, the decline (i.e., ΔSUS and ΔSWRS) was significantly greater in the symptom-positive group than in the symptom-negative group in the present study. These results suggest that patients with significantly greater worsening of SUS/SWRS after the initial

therapy developed salivary gland dysfunction during follow-up, after the second therapy. Our results therefore indicate that SGS findings after initial ^{131}I therapy can potentially predict the risk of radiation-induced salivary gland damage after continued ^{131}I therapy.

Furthermore, SUS and SWRS were shown to be independent risk factors for the development of dry mouth symptoms. While a cumulative ^{131}I dose has previously been demonstrated to be a risk factor for salivary gland dysfunction after ^{131}I therapy [2,10,16], we found that SUS and SWRS values had greater predictive ability for the development of dry mouth symptoms after ^{131}I therapy than did the cumulative ^{131}I dose. Symptomatic salivary dysfunction secondary to ^{131}I therapy could result both from a decrease in saliva production and/or secretion into the mouth. In particular, SWRS, which is reflective of salivary secretion, showed high predictive ability for dry mouth symptoms. Mandel et al. have reported that increased capillary permeability in sialadenitis enhances ^{131}I transmigration into the salivary parenchyma, while inflammation-induced duct wall damage and lumen obstruction promote ^{131}I retention [22]. Similarly, Lee et al. have shown the importance of the clearance of saliva from salivary glands into the oral cavity as a risk factor for dry mouth symptoms due to salivary gland dysfunction secondary to ^{131}I therapy [23].

On the other hand, our study did not find that ^{131}I accumulation in salivary glands on post-therapy ^{131}I scintigraphy was an independent risk factor for dry mouth symptoms. This is in contrast to a previous study that reported that symptomatic sialadenitis after radioiodine ablation could be predicted with high sensitivity by post-ablation ^{131}I whole-body scintigraphy [23]. We speculate that ^{131}I accumulation in salivary glands on post-therapy ^{131}I scintigraphy mainly reflects the acute phase of sialadenitis secondary to ^{131}I therapy. In contrast, SGS findings approximately 12 months after ^{131}I therapy reflect a relatively chronic phase of sialadenitis, which may explain the superiority of SGS findings to post-therapeutic ^{131}I scintigraphy findings in predicting dry mouth symptoms in our study.

Recently, sialoendoscopic intervention by dilating salivary ducts has been reported as treatment for chronic sialadenitis [24,25], and the intervention before salivary ducts is totally obstructed is favorable to obtain successful outcomes [24]. Early prediction of salivary gland dysfunction with dry mouth by SGS after initial ^{131}I therapy may contribute to determining indication of sialoendoscopic intervention for chronic sialadenitis.

The present study has several limitations. First, the duration between the last ^{131}I therapy and assessment of dry mouth symptoms in patients was approximately 1 year. Since salivary gland dysfunction is a late-onset complication that could develop even after 1 year, a longer follow-up period after ^{131}I therapy may be required to assess the study outcomes adequately. Second, we could not include the amount of saliva in the mouth as an objective criterion of salivary gland dysfunction, due to the retrospective nature of our study.

In conclusion, we have shown that findings from SGS after an initial ^{131}I therapy could be an effective tool for predicting the development of dry mouth symptoms secondary to high-dose ^{131}I therapy. We therefore recommend that SGS is performed in patients after initial ^{131}I therapy, particularly when repeated and high-dose ^{131}I therapy is anticipated.

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