Significance of Salivary Gland Radioiodine Retention on Post−ablation ^{131}I Scintigraphy as a Predictor of Salivary Gland Dysfunction in Patients with Differentiated Thyroid Carcinoma

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- ABSTRACT -

Significance of Salivary Gland Radioiodine Retention on Post-ablation ^{131}I Scintigraphy as a Predictor of Salivary Gland Dysfunction in Patients with Differentiated Thyroid Carcinoma

Purpose: We investigated whether ^{131}I whole-body scintigraphy could predict functional changes in salivary glands after radioiodine therapy.

Methods: We evaluated 90 patients who received initial high-dose (≥3.7 GBq) radioiodine therapy after total thyroidectomy. All patients underwent diagnostic (DWS) and post-ablation (TWS) ^{131}I whole-body scintigraphy. Visual assessment of salivary radioiodine retention on DWS and TWS was used to divide the patients into two types of groups: a DWS+or DWS-group and a TWS+or TWS-group. Salivary gland scintigraphy was also performed before DWS and at the first follow-up visit. Peak uptake and %washout were calculated in ROIs of each gland. Functional changes (Δuptake or Δwashout) of salivary glands after radioiodine therapy were compared between the two groups.

Results: Both peak uptake and the %washout of the parotid glands were significantly lower after radioiodine therapy (all p values <0.001), whereas only the %washout were significantly reduced in the submandibular glands (all p values <0.05). For the parotid glands, the TWS+ group showed larger Δuptake and Δwashout after radioiodine therapy than did the TWS- group (all p values <0.01). In contrast, the Δuptake and Δwashout of the submandibular glands did not significantly differ between the TWS+ and TWS- groups (all p values >0.05). Likewise, no differences in Δuptake or Δwashout were apparent between the DWS+ and DWS- groups in either the parotid or submandibular glands (all p values >0.05).

Conclusion: Salivary gland radioiodine retention on post-ablation ^{131}I scintigraphy is a good predictor of functional impairment of the parotid glands after high-dose radioiodine therapy.

Keyword: Radioiodine therapy, Salivary gland dysfunction, Differentiated thyroid cancer, ^{131}Iscintigraphy, Salivary gland scintigraphy.

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Ⅰ. Introduction

The management of patients with well-differentiated thyroid carcinomas includes surgical removal of all tumor tissue followed by radioactive iodine ^{131}I therapy. Postoperative ^{131}I therapy is used to destroy remnant thyroid tissue as well as microscopic metastases, and affords the benefits of significant reductions in recurrence and cancer mortality rates in patients with papillary or follicular thyroid cancer(Mazzaferri and Jhiang, 1994; Schlumberger, 1998). It has also been reported that ^{131}I therapy improved the 5-year recurrence-free survival rates even of patients with papillary microcarcinoma (Creach et al, 2012). Furthermore, administration of a therapeutic dose of ^{131}I enables visualization of persistent tumor tissue, via highly sensitive whole-body scanning, in patients with elevated levels of serum thyroglobulin(Lind, 1999).

However, although high-dose ^{131}I therapy prolongs survival, some side effects are apparent. Alexander et al. reported that ~77% of patients reported intermediate or long-term complaints including sialadenitis, transient loss of taste or smell, transient alopecia, chronic/recurrent conjunctivitis, increased frequency of influenza infection and hematologic abnormalities(Alexander et al, 1998). Apart from these side effects, high-dose ^{131}I therapy can impair dental health by increasing the risk of caries and the need for tooth extractions(Walter. 1998). Of the problems listed above, sialadenitis is the most frequent complication, associated with radiation damage caused during the transport of radioiodine into the salivary glands, which have an iodide uptake mechanism similar to that of the thyroid, and concentrate iodine to levels 20 - 100-fold that in serum. The frequency of intermediate sialadenitis was initially ~33% and reached 43% 1 year after treatment(Allweiss et al, 1984; Cavalieri, 1997; Alexander et al, 1998; Mandel S.J and Mandel L., 2003). The frequency of radiation-induced sialadenitis is dose-dependent, being proportional to the cumulative ^{131}I dose administered(Spitzweg et al, 2001; Hyer et al, 2007; Kim et al, 2007; Macioszek et al, 2008). However, in more than half of all cases, reduced salivary gland function was not obviously associated with clinically evident xerostomia or post-therapeutic sialadenitis(Alexander et al, 1998). Therefore, predicting the occurrence of salivary gland dysfunction is of great importance in the management of patients with differentiated thyroid cancer.

Salivary gland scintigraphy using ^{99m}Tc-pertechnetate can assess functional damage to the glands following radioiodine therapy(Malpani et al, 1996; Caglar et al, 2002). Intravenously administered ^{99m}Tc-pertechnetate gradually accumulates in the salivary glands over 20min post-administration and is then excreted as saliva production is enhanced. This type of scintigraphy yields semiquantitative data on uptake ratios and %excretion values(Raza et al, 2006; Kang et al, 2011; An et al, 2013). However, no reliable method has yet been developed to predict functional impairment of salivary glands at the time of ^{131}I ablation therapy.

Diagnostic ^{131}I whole-body scintigraphy (DWS) can be used to acquire information on the presence of iodine-avid remnant thyroid tissue and also to detect locoregional or distant metastases(Cooper et al, 2009). Post-ablation ^{131}I whole-body scintigraphy (TWS) is also useful in this context, particularly in patients with elevated serum thyroglobulin levels, because TWS is more sensitive than DWS when used to detect metastatic disease(Lind, 1999; Chong et al, 2010). Our clinical experience has taught us that some patients exhibit ^{131}I retention in the salivary glands on either DWS or TWS. We conducted the present study to explore whether salivary retention evident on whole-body scintigraphy at the time of ^{131}I ablation could predict functional impairment of the salivary glands in patients with papillary thyroid cancer.

Ⅱ. Materials and Methods

A. Subjects

Study subjects were recruited by review of medical records from June 2010 to October 2011. During this period, a total of 229 patients were referred for ^{131}I ablation therapy to treat differentiated thyroid cancer. Of these patients, those who met the following criteria were selected: (1) the first course of radioiodine therapy was given after total thyroidectomy; (2) treatment featured high-dose ^{131}I therapy (≥3.7GBq); (3) both DWS and TWS were performed; (4) salivary gland scintigraphy was performed both before and after radioiodine therapy. We limited our subjects using criterion (1) above because some patients already had salivary gland dysfunctions, caused by previous therapy, at the time when the second course of radioiodine therapy was given, or thereafter. Eighteen patients who had undergone low-dose (1.1GBq) ^{131}I therapy were also excluded from the study because radiation-induced sialadenitis rarely occurs in such patients. Furthermore, DWS was frequently not performed on such patients. Another four patients excluded from the study had undergone high-dose radiotherapy (5.5 or 7.4 GBq) without performance of DWS. Initially, they were scheduled for low-dose radioiodine therapy, but the doses were raised because of elevations in serum thyroglobulin concentrations.

Information on patients' characteristics, including symptoms of salivary dysfunction and the details of radioiodine ablation therapy, was collected retrospectively via medical record review. Pain and/or swelling in a salivary gland, and a dry mouth, were considered to be symptoms of salivary dysfunction(Hyer et al, 2007).

B. Radioiodine Treatment Protocol

The radioiodine ablation protocol is shown in Figure 1. Four weeks before administering ^{131}I, patients were requested to stop taking levothyroxine (T4) and to switch to triiodothyronine (T3). Any form of thyroid hormone supplementation was prohibited from 2 weeks prior to radioiodine therapy, and, at the same time, patients were instructed to start taking a low-iodine diet. Eight days before radioiodine therapy, blood was withdrawn for measurement of thyroid-stimulating hormone and thyroglobulin levels and, on the same day, baseline salivary gland scintigraphy was performed. DWS was acquired 2 days after administration of 74 MBq ^{131}I. ^{131}I ablation therapy was performed on the first day of hospitalization and patients were encouraged to drink 2 L of water daily and to take sialogogues containing vitamin C. TWS was obtained 1 week after radioiodine therapy. All patients underwent post-treatment salivary gland scintigraphy at their first follow-up visits after discharge.

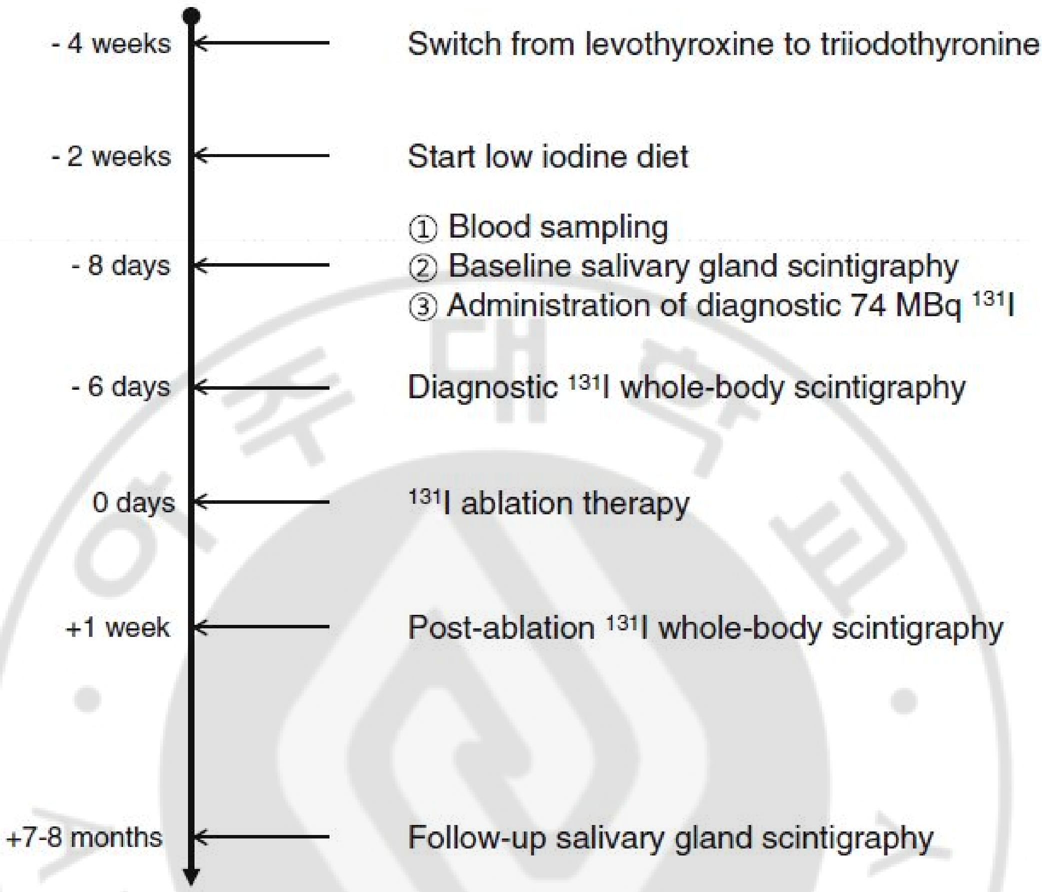

Fig. 1. Flow diagram showing the process of radioiodine therapy

C. Acquisition and Image Analysis of Salivary Gland Scintigraphy

Salivary gland scintigraphies were acquired using dual-head ɣ-cameras (Infinia Hawkeye 4, GE Healthcare, Milwaukee, WI; or Varicam, Elscint, Haifa, Israel) equipped with low-energy high-resolution collimators. In the supine position, each patient received an intravenous injection of 185 MBq of ^{99m}Tc-pertechnetate, and static anterior and lateral images (from both sides) of the head-and-neck region were acquired 5, 10, 15, and 20 min later. Immediately after acquisition of the 20-min images, 200 ml of orange juice was given orally to stimulate saliva production, and 40-min images were later acquired. Each image was stored in a 128×128 matrix for 1 min. For quantitative analysis, polygonal regions of interest (ROIs) were drawn over the parotid and submandibular glands visible on anterior images (Figure2). On the same images, a circular ROI was placed over the skull, to allow of background correction. ^{99m}Tc-pertechnetate uptake was calculated as the ratios of the average radioactivity of the salivary gland to that of the background. Peak uptake was defined as the highest such value noted on the 5-to-20-min images. Percentage washout of salivary glands was calculated as the proportions of cleared radioactivity (peak radioactivity minus the radioactivity at 40min) divided by peak radioactivity. The lateral difference was assessed by comparing peak uptake and %washout between right and left paroid glands and between right and left submandibular glands. To evaluate the effect of radioiodine ablation on salivary gland function, peak uptake and %washout of each gland were compared between baseline and follow-up scintigraphies. Functional changes in salivary glands after radioiodine therapy were quantitated as Δpeak or Δwashout:

Δpeak = peak uptake upon follow-up salivary gland scintigraphy minus peak uptake upon baseline salivary gland scintigraphy

Δwashout = %washout upon follow-up salivary gland scintigraphy minus %washout upon baseline salivary gland scintigraphy

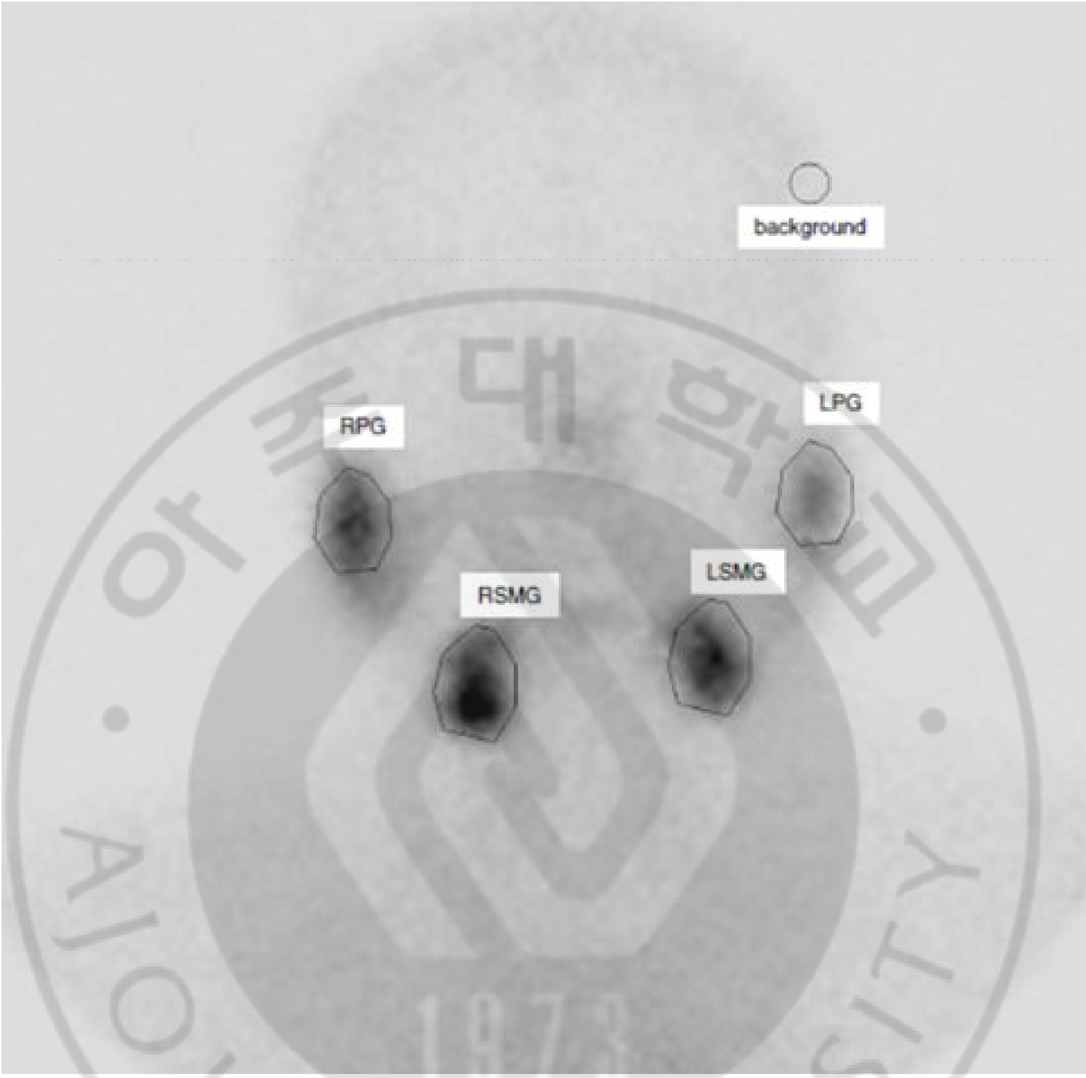

Fig. 2. Polygonal region of interests (ROIs) were drawn over bilateral paotid and submandibular glands. A circular ROI was placed over the skull for the correction of background activity.

D. Acquisition and Image Analysis of ^{131}I Whole-Body Scintigraphy

Whole-body scintigraphies were acquired using dual-head γ-cameras

(Infinia Hawkeye 4, GE Healthcare, Milwaukee, WI; or Varicam, Elscint, Haifa, Israel) equipped with medium-energy collimators (peak, 364 keV; window, 15%). Both anterior and posterior planar images, from the vertex to the knee, were obtained and stored in 256×1,024 matrices, using a scan speed of 9 cm/min. Scintigraphies were retrospectively reviewed by two nuclear medicine physicians (J.K.Y and K.S.C) blinded to patient data, and the presence or absence of radioiodine retention in salivary glands was determined visually by consensus. Using the scintigraphic data, each gland was classified by radioiodine retention status as either DWS+ or DWS− group and either TWS+ or TWS− group. The Δpeak and Δwashout of each gland were compared between the two groups to evaluate the significance of radioiodine retention on functional changes to the salivary glands after radioiodine therapy.

E. Statistical Analysis

The t-test was used to compare peak uptake, %washout, Δpeak, and Δwashout before and after radioiodine therapy, and between the two groups. The chi-squared test was used to compare the frequency of radioiodine retention on DWS and TWS. All statistical analyses were performed using the MedCalc software (version 12.3.0; MedCalc, Mariakerke, Belgium). P values less than 0.05 were considered to reflect significance.

Ⅲ. Results

A. Characteristics of Patients

Our final study population contained 90 patients with papillary thyroid cancer (23 males, 67 females; mean age 48 years; range, 23-70 years). Half (n=45) of all patients complained of at least one salivary symptom at the time of follow-up salivary scintigraphy. Most patients (93.3 %, 84/90) received either 3.7 or 5.6 GBq of radioiodine (mean dose 5.0 GBq; range, 3.7-9.3 GBq). The mean interval from baseline to follow-up salivary scintigraphy was 223 days, and the interval for most patients (87.8 %, 79/90) was less than 9 months. Table 1 details the characteristics of patients.

Table 1. Characteristics of patients

Variables	Values
Total number of patients	90
Male/female	23/67
Age (years)	48±12 (23-70)
Duration (days)	
From baseline to follow-up salivary gland scintigraphy	223±55 (164-421)
From diagnostic ^{131}I whole-body scintigraphy to ^{131}I ablation therapy	6±1 (4-12)
From ^{131}I ablation therapy to post-ablation ^{131}I whole-body scintigraphy	7±1 (2-9)
Symptoms of salivary gland dysfunction (pain, swelling or dry mouth)	50% (45/90)
Dose of ^{131}I ablation therapy	
Mean	5.0±1.3 (GBq)
3.7/5.6/7.4/9.3 (GBq)	42/51/3/3%

Mean±SD; GBq, gigabecquerel

B. Salivary Gland Function

All salivary glands showed ^{99m}Tc-pertechnetate uptake peaks at either 15 or 20 min (data not shown). Table 2 presents data on salivary gland function evaluated by salivary gland scintigraphy before and after ^{131}I ablation therapy. There was no lateral difference in the peak uptake of either the parotid or submandibular glands on either baseline or follow-up salivary gland scintigraphy (all p values >0.05). However, %washout was slightly lower in right-sided than in left-sided glands (for parotid glands: 39.8±17.1% vs. 42.8±15.6%, p=0.0013; and for submandibular glands: 38.7±13.0% vs. 40.3±12.1%, p=0.0156). However, after ^{131}I ablation therapy, these differences were no longer apparent (all p values >0.05).

After high-dose ^{131}I ablation therapy, the parotid glands showed significant reductions in both peak uptake (5.68±1.69 → 4.91±1.65, p<0.0001) and %washout (41.3±16.4% → 27.1±26.8%, p<0.0001), whereas, for submandibular glands, only %washout was significantly reduced (39.5±12.6% → 30.9±26.9%, p=0.0001). Unlike the parotid glands, the peak uptake of the submandibular glands was not significantly reduced by ^{131}I ablation therapy (4.01±1.19 → 3.95±0.98, p=0.4827). Consequently, larger decrease in peak uptake was observed in the parotid than the submandibular glands (Δpeak=−0.77±1.86 vs. −0.06±1.22, p<0.0001), while the extent of functional decrease in %washout was similar between the parotid and submandibular glands (Δwashout= −14.1±32.0 % vs. −8.6±29.8 %, p=0.091).

Table 2. Salivary gland function before and after ^{131}I ablation therapy

	Peak uptake			*p value	%Washout			*p value
	Before	After	Δpeak		Before	After	Δpeak	
RPG	5.64±1.75	4.84±1.72	−0.79±1.89	***0.0001***	39.8±17.1%	26.4±29.8%	−13.3±35.9%	***0.0007***
LPG	5.72±1.64	4.98±1.57	−0.75±1.83	***0.0002***	42.8±15.6%	27.8±23.5%	−14.9±27.8%	***<0.0001***
Total	5.68±1.69	4.91±1.65	−0.77±1.86	***<0.0001***	41.3±16.4%	27.1±26.8%	−14.1±32.0%	***<0.0001***
RPG	4.01±1.13	3.95±0.97	−0.06±1.24	0.6578	38.7±13.0%	30.6±28.3%	−8.1±31.2%	***0.0156***
LPG	4.01±1.25	3.94±0.98	−0.07±1.21	0.5844	40.3±12.1%	31.2±25.5%	−9.1±28.4%	***0.0031***
Total	4.01±1.19	3.95±0.98	−0.06±1.22	0.4827	39.5±12.6%	30.9±26.9%	−8.6±29.8%	***0.0001***

Mean±SD; *p value means statistical significance of the difference in peak uptake or %washout between before and after 131I therapy; RPG, right parotid gland; LPG. left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland.

C. Radioiodine Retention on ^{131}I Whole-Body Scintigraphy

Totals of 180 parotid and 180 submandibular glands from 90 patients were examined. DWS revealed radioiodine retention by 28.9% (52/180) of parotid glands and 28.9% (52/180) of submandibular glands (Table 3), and no significant differences in the proportions of radioiodine retention were evident among the four glands (p>0.05). On TWS, the frequency of radioiodine retention was different among the four glands (p<0.005) where it was observed more frequently in submandibular than parotid glands (39.4% vs. 20.0%, p<0.001). Thus, each gland was identified as DWS+ or DWS− and TWS+ or TWS−.

Table 3. Salivary gland radioiodine retention on diagnostic or post-ablation ^{131}I whole-body scintigraphy

Radioiodine retention		DWS				TWS			
		RPG	LPG	RSMG	LSMG	RPG	LPG	RSMG	LSMG
(+)		25	27	27	25	20	18	35	36
(−)		65	63	63	65	70	72	55	54
*p value	Among the four glands	>0.05				***<0.005***			
	PG vs. SMG	>0.05				***<0.001***			

*p value means statistical significance of the difference in the frequency of radioiodine retention. The frequency of radioiodine retention was compared among the four glands, and it was then compared between the parotid and submandibular glands. DWS, diagnostic ^{131}I whole-body scintigraphy; TWS, post-ablation ^{131}I whole-body scintigraphy; RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland; PG, parotid gland; SMG, submandibular gland

D. Relation between Radioiodine Retention and Salivary Gland Function

After classification into the subgroups described above, it was apparent that the peak uptake of the parotid gland was decreased by ^{131}I therapy in both the DWS+ and DWS− groups, but the Δpeak did not significantly differ between the two groups (1.02±2.26 vs. 0.67±1.67, p=0.3207, Table 4). Likewise, the falls in %washout of both the parotid and submandibular glands did not differ between the DWS+ and DWS− subgroups (all p values >0.05). On the other hand, the peak uptake of the submandibular gland changed minimally after ^{131}I therapy, and no significant difference in Δpeak was apparent between the DWS+ and DWS- groups (*p*=0.0586). Therefore, neither peak uptake nor %washout correlated with radioiodine retention, as revealed by DWS, by either the parotid or submandibular glands.

In contrast, after ^{131}I therapy, the fall in peak uptake of the parotid gland was greater in the TWS+ than in the TWS- group (Δpeak=1.63±2.12 vs. 0.54±1.71, *p*=0.0053, Table5). Similarly, the %washout of the parotid gland decreased to a greater extent in the TWS+ than the TWS-group (Δwashout=33.4±44.6% vs. 9.0±25.5%, *p*=0.0023). However, as was noted when DWS data were examined, the submandibular gland exhibited a minimal decrease in peak uptake that was not accompanied by any difference in Δpeak (-0.13±1.06 vs. 0.19±1.31, *p*=0.0678). In addition, Δwashout did not differ between the TWS+ and TWS-groups (4.2±20.0% vs. 11.5±34.5%, p=0.0719). Therefore, radioiodine retention as revealed by TWS was closely related to functional changes in the parotid, but not the submandibular, glands.

Table 4. Relation between the radioiodine retention on diagnostic ^{131}I whole-body scintigraphy and the functional change of salivary gland

			Peak uptake				%Washout			
		N	Before ^{131}I therapy	After ^{131}I therapy	Δpeak	*p value	Before ^{131}I therapy	After ^{131}I therapy	Δwashout	*p value
PG	DWS+	52	6.05±1.73	5.03±1.87	1.02±2.26	0.3207	45.0±16.3%	24.7±35.3%	20.3±42.0%	0.1693
	DWS−	128	5.53±1.66	4.86±1.55	0.67±1.67		39.7±16.3%	28.1±22.5%	11.6±26.7%	
SMG	DWS+	52	3.56±0.81	3.74±0.75	−0.18±0.99	0.0586	38.4±10.4%	32.4±18.4%	6.0±18.8%	0.3456
	DWS−	128	4.20±1.26	4.03±1.04	0.16±1.29		40.0±13.4%	30.3±29.7%	9.7±33.2%	

Mean±SD; N, number of gland; *p value means statistical significance of the difference in Δpeak or Δwashout between DWS+ and DWS−; Δpeak, net difference in peak uptake between baseline and follow-up salivary scintigraphy; Δwashout, net difference in %washout between baseline and follow-up salivary scintigraphy; PG, parotid gland; SMG, submandibular gland; DWS+, patients with retention on diagnostic ^{131}I whole-body scintigraphy; DWS−, patients without retention on diagnostic ^{131}I whole-body scintigraphy.

Table 5. Relation between the radioiodine retention on post-ablation ^{131}I whole-body scintigraphy and the functional change of salivary gland

			Peak uptake				%Washout			
		N	Before ^{131}I therapy	After ^{131}I therapy	Δpeak	*p value	Before ^{131}I therapy	After ^{131}I therapy	Δwashout	*p value
PG	TWS+	52	6.02±1.83	4.39±1.74	1.63±2.12	*0.0053*	42.6±17.4%	9.2±38.0%	33.4±44.6%	*0.0023*
	TWS−	128	5.59±1.65	5.05±1.60	0.54±1.71		40.9±16.2%	31.9±20.6%	9.0±25.5%	
SMG	TWS+	52	3.81±1.16	3.94±0.97	−0.13±1.06	0.0678	36.8±10.6%	32.6±19.7%	4.2±20.0%	0.0719
	TWS−	128	4.14±1.19	3.95±0.99	0.19±1.31		41.3±13.5%	29.8±30.7%	11.5±34.5%	

Mean±SD; N, number of gland;*p value means statistical significance of the difference in Δpeak or Δwashout between TWS+ and TWS−; Δpeak, net difference in peak uptake between baseline and follow-up salivary scintigraphy; Δwashout, net difference in %washout between baseline and follow-up salivary scintigraphy; PG, parotid gland; SMG, submandibular gland; TWS+, patients with retention on postablation ^{131}I whole-body scintigraphy; TWS−, patients without retention on post-ablation ^{131}I whole-body scintigraphy.

Ⅳ. Discussion

Sialadenitis is the most prevalent complication in patients who undergo radioiodine therapy to treat differentiated thyroid carcinoma. Most such conditions can be relieved by conservative treatment featuring adequate hydration; salivary flow stimulation, external compression, and medication including NSAIDs, anticholinergics, or steroids. However, in some cases, invasive procedures are required, for example, sialendoscopy or surgical removal of a salivary gland, and permanent damage to the salivary glands results(Raza et al, 2006; Kim et al, 2007; Prendes et al, 2013). Salivary glands cause pain and swelling as early as a few days after radioiodine therapy. However, such early symptoms are frequently transient and subside spontaneously; they are thus not reliable predictors of permanent salivary gland dysfunction(Mandel S.J and Mandel L., 2003). In a previous study by Macioszek et al., the acute sialadenitis symptoms developing after radioiodine therapy were not correlated with subsequent salivary gland dysfunction(Macioszek et al, 2008). However, prediction of salivary gland dysfunction is crucial to select patients who require close observation after treatment and to reduce the extent of such dysfunction. In this study, we investigated whether salivary gland radioiodine retention, as revealed by ^{131}I whole-body scintigraphy, could be used to predict functional salivary gland impairment caused by radioiodine therapy.

Our data show that the extent of functional changes in the parotid glands after radioiodine therapy was greater in the TWS+ than in the TWS- group in terms of both peak uptake and %washout. This indicates that parotid gland radioiodine retention on TWS is closely associated with development of later salivary dysfunction, and such patients therefore require more aggressive management, and close observation to protect the salivary glands. In contrast, neither the peak uptake nor %washout of the submandibular glands differed significantly between the TWS+ and TWS- groups. This implies that submandibular gland dysfunction cannot be predicted by radioiodine retention revealed by TWS. A possible explanation for the differences in these results is the fact that the histology of the salivary glands differs. Parotid glands are serous cell-dominant and are affected more by radiation than are mucous cells. However, the submandibular glands are composed of both mucous and serous cells. In addition the parotid gland transports more radioiodine than does the submandibular gland. Therefore, it is understandable that the parotid gland should be more susceptible to radiation-induced damage than the submandibular gland, in patients receiving ^{131}I ablation therapy(Rigler and Scanlon, 1955; Malpani et al, 1996; Mandel S.J and Mandel L., 2003). Esfahani et al. reported that the decrease in the proportion of saliva secreted by the parotid glands was greater than that from the submandibular glands, as revealed by salivary gland scintigraphy, at both 3 weeks and 3 months after radioiodine ablation therapy(Esfahani et al, 2004). Macioszek et al. evaluated salivary gland function by calculating radioiodine uptake ratios, and parotid radiosensitivity was evident(Macioszek et al, 2008). A study of a Korean population by Kim et al. also indicated that the incidence of salivary gland symptoms was higher in parotid (90%, 19/21) than submandibular glands (10%, 2/21)(Kim et al, 2007). Lee et al. showed that the estimated absorbed doses upon radioiodine therapy were similar for both the parotid and submandibular glands (2.7±0.8 Gy and 2.8±1.1 Gy, respectively)(Lee et al, 2013). All of these data are in agreement with our finding that the parotid glands are highly susceptible to radiation damage. As shown in Table2, the peak uptake of the parotid glands was decreased significantly after ^{131}I

ablation therapy, but this was not the case with the submandibular glands. Turning to %washout, both the parotid and submandibular glands exhibited significant reductions in these vales after ^{131}I ablation therapy, but the extent of reduction was greater in the parotid than the submandibular glands. Also, these data were collected under conditions in which radioiodine accumulated to higher levels in the submandibular glands (Table3). Therefore, in the clinic, it is possible to predict functional changes caused by radioiodine therapy only for the parotid gland.

Lee et al. (2013) suggested recently that post-ablation ^{131}I whole-body scintigraphy may be used to predict the development of symptomatic sialadenitis after radioiodine ablation. In the cited study, patients with symptomatic sialadenitis exhibited higher levels of ^{131}I uptake by the parotid glands on early (day3) ^{131}I scintigraphy. Visual and semiquantitative evaluation allowed prediction of the development of sialadenitis after radioiodine ablation, with sensitivities ranging from 80-93%. In contrast, ^{131}I uptake did not differ significantly in the submandibular gland or upon delayed (day7) ^{131}I scintigraphy. In some respects, the findings of our present study differ from those of Lee et al. The cited authors monitored the development of symptomatic sialadenitis, but we evaluated salivary gland function using ^{99m}Tc-pertechnetate salivary gland scintigraphy. In addition, Lee et al. monitored symptoms of sialadenitis (pain/swelling of salivary glands, taste loss, dry mouth, and xerostomia) in both the acute (hospitalization) and chronic (on follow-up visits at intervals of 1-6 months) periods. Hence, the cited study examined both acute and chronic sialadenitis. However, in our present study, we focused on chronic salivary gland dysfunction, because it is known that development of acute sialadenitis is not associated with later salivary gland dysfunction(Mandel S.J. and Mandel L., 2003). Finally, the cited authors found that only early scintigraphy could be used to predict the occurrence of sialadenitis. On the contrary, we found that delayed scintigraphy predicted more severe salivary gland dysfunction. However, despite the differences between the two studies, the finding of the cited work, to the effect that post-ablation scintigraphy can be used to predict salivary gland functional impairment, is in line with the results of the present study.

As expected, DWS was ineffective in terms of predicting functional impairment caused by radioiodine therapy (Table 4). After classification of salivary glands into DWS+ and DWS- groups, based on radioiodine retention, the parotid glands showed no significant differences in terms of Δpeak and Δwashout between the two groups. The same was true of Δwashout of the submandibular glands. Also, no significant decrease was observed in peak uptake of the submandibular glands. To minimize the stunning effect, DWS is performed in our clinic using 74 MBq [^{131}I](Woolfenden, 2006), which is too small a dose to injure the salivary gland. which is too small a dose to injure the salivary gland. Two case reports on salivary gland ^{131}I uptake, shown by ^{131}I whole-body scintigraphy, in patients with sialadenitis have appeared. Kolla et al. described a 53-year-old patient exhibiting focal ^{131}I uptake on follow-up diagnostic ^{131}I scintigraphy, which mimicked nodal metastasis, but proved to be chronic submandibular sialadenitis after radioiodine therapy(Kolla et al, 1989). Carlisle et al. also observed bilateral parotid ^{131}I uptake on follow-up diagnostic ^{131}I scintigraphy in a patient with radioiodine therapy-induced chronic parotitis(Carlisle and McDougall, 2000). These reports suggested that ^{131}I uptake revealed by ^{131}I scintigraphy was indicative of the presence of sialadenitis. However, the results of the present study suggest that DWS data cannot be used to predict salivary gland dysfunction caused by ^{131}I ablation therapy.

As shown in Table 3, the pattern of radioiodine retention revealed by DWS was different from that shown on TWS. Although the radioiodine accumulation by the four salivary glands did not differ upon DWS, we found that the submandibular glands accumulated more radioiodine on TWS. However, the reason for this difference in the pattern of radioiodine retention is uncertain. A possible contributing factor is the difference in the radioiodine dose used for scintigraphy. As submandibular glands produce more saliva than parotid glands, it would appear quite reasonable that submandibular glands accumulate more radioiodine on TWS. However, on DWS, most of the administered radioiodine is taken up by remnant thyroids, and very little of that is circulating in the blood. Consequently, the difference in radioiodine concentration between parotid and submandibular glandsmay not be evident. Even though we used a very low dose of radioiodine for DWS, all images demonstrated the body contour clearly from vertex to mid-thigh. Thus, this difference would not result from the image quality of those scintigraphies.

Table 2 shows the functional status of the parotid and submandibular glands as evaluated by ^{99m}Tc-pertechnetate salivary gland scintigraphy. Although both peak uptake and %washout of the parotid gland were reduced significantly by radioiodine therapy, only %washout in the submandibular glands was decreased significantly. As mentioned above, the submandibular gland is more resistant than the parotid gland to radiation-induced damage because of histological differences between the two glands(Esfahani et al, 2004; Kim et al, 2007). The difference in the time of onset of damage may also explain our observations. ^{99m}Tc-pertechnetate uptake by the salivary gland, and washout thereof, reflect parenchymal and ductal functions, respectively. As radiation causes damage first to the ductal walls, followed by later vascular fibrosis(Mandel S.J. and Mandel L., 2003), salivary excretion could be impaired earlier, and to a great erextent, than parenchymal uptake, at early time points. Parenchymal impairment would have been more prominent had the patients been followed up over a longer period.

The present study was retrospective in nature, and the time between baseline and follow-up salivary gland scintigraphy varied from 5.5 to 14 months. It is known that the propensity for development of radiation-induced side effects may change with the duration of follow-up(Alexander et al, 1998). In the current study, most patients (87.8%) visited our hospital about 7 months (5.5-9 months) after radioiodine ablation; however, some variation in visit time was inevitable. Moreover, we evaluated all patients only once after they received therapy. When it is considered that both the incidence and pattern of salivary gland dysfunction can change even after 1 year of therapy, it is clear that further clinical observations are needed. Another limitation of our study is that the extent of radioiodine retention upon ^{131}I whole-body scintigraphy was assessed visually; we did not explore any possible correlation between the level of radioiodine retention and the extent of functional damage to the salivary glands. As the extent of radioiodine retention was arbitrarily graded from 1 to 3, most cases were assigned to grade 1. Therefore, we simply classified patients into two groups, characterized by the 'presence' or 'absence' of retention. Finally, our study population was small; thus, the post-ablation status of the salivary glands was assessed semiquantitatively using scintigraphy. However, if the symptoms of sialadenitis are considered, it would be possible to subdivide patients into a normal group, a group with chronic sialadenitis and permanent salivary dysfunction. Therefore, further study using larger populations to allow patient sub-classification and longer-term observations is required in future.

V. Conclusion

In conclusion, radioiodine retention by the parotid glands upon post-ablation ^{131}I whole-body scintigraphy was associated with reductions in peak uptake and %washout after radioiodine therapy in patients with differentiated thyroid carcinoma. Post-ablation ^{131}I whole-body scintigraphy may be used to predict severe functional impairment of the parotid glands, thus identifying patients requiring close observation and aggressive preventative measures.

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- 국문요약 -

방사성 요오드 치료를 받은 분화성 갑상선암 환자의 전신 요오드 스캔 상 관찰되는 침샘 섭취와 타액선 기능 변화의 연관성

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분화성 갑상선암으로 방사성 요오드 치료를 받은 환자에서 전신 요오드 스캔을 통한 타액선 기능 변화 예측이 가능한지 알아보고자 하였다. 2010년 6월부터 2011년 10월까지 분화성 갑상선암으로 갑상선 전절제술 후 첫번째 고용량 방사성 요오드 치료를 받은 환자 중, 진단 및 치료 후 전신 요오드 스캔과 치료 전후 두 차례의 타액선 섬광조영술 모두를 시행한 90명의 환자를 대상으로 하였다. 이 환자들의 진단 및 치료 후 전신 요오드 스캔 상 관찰되는 타액선 부위의 섭취증가 유, 무에 따라 각각 두 가지 그룹으로 분류하였으며, 치료 전후의 타액선 섬광조영술을 통하여 이하선 및 악하선의 섭취율 및 배설율의 변화를 알아보았다. 전신 요오드 스캔에서 관찰되는 타액선 부위의 섭취증가와 방사성 요오드 치료 후 타액선 기능 변화 사이의 연관성에 대해 분석한 결과, 치료 후 전신 요오드 스캔에서 이하선 부위에 섭취증가를 보이는 환자군의 경우 섭취증가를 보이지 않는 환자군에 비해 방사성 요오드 치료 후 이하선의 섭취율 및 배설율이 유의하게 감소한 반면, 악하선 부위의 섭취증가 유무는 타액선 기능변화와 별다른 관계가 없었다. 이와 마찬가지로, 진단 전신 요오드 스캔에서 관찰되는 이하선 및 악하선 부위의 섭취증가는 치료 후 타액선 기능 변화와 연관성이 없었다. 따라서 고용량 방사성 요오드 치료 후 전신 요오드 스캔에서 이하선 부위에 섭취증가를 보이는 환자의 경우 이하선의 기능저하를 예측할 수 있으며 이를 통해

타액선 기능 변화에 대한 적절한 예방 및 치료에 도움이 될 것으로 사료된다.

핵심어: 방사성 요오드 치료, 타액선 기능 변화, 분화성 갑상선암, 전신 요오드 스캔, 타액선 섬광조영술