Quantitative Evaluation of Salivary Gland Scintigraphy in Sjögren's Syndrome

Isao Umehara, Ichiro Yamada, Yuji Murata, Yuzo Takahashi, Norihiko Okada and Hitoshi Shibuya

Department of Radiology, Faculty of Medicine, and Departments of Oral Surgery and Clinical Laboratory, Faculty of Dentistry, Tokyo Medical and Dental University, Tokyo, Japan

This study compared the quantitative characteristics of salivary gland scintigraphy in patients with Sjögren's syndrome with the histopathologic grading of labial biopsy. **Methods:** Thirty-nine patients with Sjögren's syndrome were studied by salivary gland scintigraphy and labial biopsy. Twelve normal volunteers were also studied as a control group for scintigraphic parameters. After injection of 370 MBq ^{99m}Tc sodium pertechnetate, dynamic salivary scintigraphy with lemon juice stimulation was performed for 50 min. Functional parameters for the parotid and submandibular glands were calculated, and scintigraphic and histopathologic results were compared. **Results:** With the progression of histopathologic grades 1–4, the velocity of tracer secretion decreased in the parotid gland ($P < 0.05$), and the quantity of tracer accumulation decreased in the submandibular gland ($P < 0.05$). The histopathologic grade in patients with Sjögren's syndrome was correlated with these scintigraphic parameters ($P < 0.05$): Histopathologic grade = 2.304 − 0.014 × (submandibular gland maximum accumulation) + 0.196 × (parotid gland time interval of tracer secretion). **Conclusion:** Decreased secretion velocity in the parotid gland and decreased accumulation in the submandibular gland were sensitive indicators of salivary gland disease in Sjögren's syndrome. The histopathologic grade was correlated with these scintigraphic parameters.

Key Words: salivary gland scintigraphy; Sjögren's syndrome; labial biopsy

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Sjögren's syndrome is an autoimmune disease affecting salivary and lacrimal glands (*1,2*). Xerostomia is the most common oral symptom in patients with Sjögren's syndrome. For diagnosis and evaluation of Sjögren's syndrome an objective examination method is required, since patient complaints do not necessarily reflect the severity of salivary gland disease.

Labial salivary gland biopsy is a reliable and useful but very invasive method for diagnosing Sjögren's syndrome (*3,4*). Recently, salivary gland scintigraphy with ^{99m}Tc sodium pertechnetate has been used to evaluate salivary gland function in xerostomic patients (*4–13*). This scintigraphy is an easy and noninvasive method to evaluate bilaterally both parotid and submandibular glands, but no standard method for Sjögren's syndrome has been established. In addition, to our knowledge, no report has dealt with the relationship between quantitative scintigraphic parameters and histopathologic grades.

In this study we compared quantitative parameters of salivary gland scintigraphy with histopathologic grades at labial salivary gland biopsy in patients with Sjögren's syndrome. From these data we have determined useful scintigraphic parameters for evaluation of salivary gland disease and calculated an equation to correlate salivary gland disease with scintigraphic parameters.

MATERIALS AND METHODS

Patients

The retrospective study included 39 consecutive patients in our institution with xerostomia (37 women and 2 men; mean age 54 y; range, 24–74 y) who were clinically diagnosed as having Sjögren's syndrome. All patients underwent both salivary gland scintigraphy and labial biopsy in our institution. As a control group for scintigraphic parameters, we included 12 normal volunteers (4 men and 8 women; mean age 49 y; range, 18–67 y).

Imaging Examinations

After intravenous injection of 370 MBq ^{99m}Tc sodium pertechnetate, dynamic salivary gland scintigraphy was performed with a gamma camera and data analysis system (PRISM 2000 and ODYSSEY; Shimadzu, Kyoto, Japan), using a low-energy, high-sensitivity, parallel-hole collimator and 140 keV photopeak for ^{99m}Tc. Anterior sequential salivary gland images were obtained at 20 s per frame for 50 min. Forty minutes after the injection, 2 mL of lemon juice were administered intraorally as a stimulus.

Data Analysis

On all summation images, oval-shaped regions of interest (ROIs) were marked over each of the parotid and submandibular glands. Background ROIs were marked in the temporal and submental regions near the parotid and submandibular glands, respectively (Fig. 1). A time-activity curve of each salivary gland was drawn using background subtraction and three-point smoothing. As shown in Figure 2, the following points were designated on the time-activity curve: point A, the initial shoulder, representing a vascular perfusion, or in cases of an unclear shoulder, at 1 min; point B, the maximum count; point C, the stimulation point at 40

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For correspondence or reprints contact: Ichiro Yamada, MD, Department of Radiology, Faculty of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.

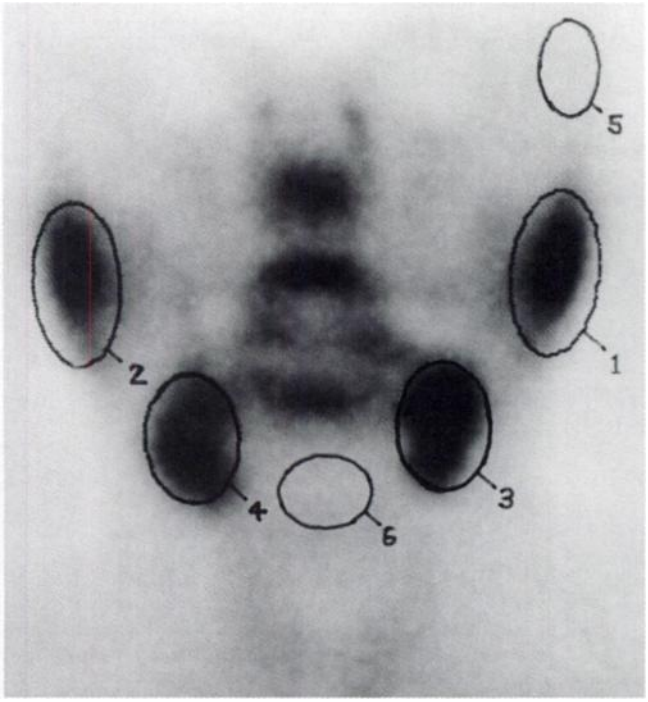

FIGURE 1. Regions of interest in scintigraphic image. Areas 1 and 2, parotid glands; areas 3 and 4, submandibular glands; area 5, background for parotid glands; and area 6, background for submandibular glands.

min; and point D, the minimum count after stimulation. Moreover, the counts specified as a, b and d, were defined by the counts at points A, B and D, respectively.

On the basis of these ROI counts on the time-activity curve, the following functional parameters (Table 1) were calculated for each salivary gland: uptake ratio (UR), T_{max}, T_{min}, maximum accumulation (MA) and maximum secretion (MS). Mean values of the bilateral glands were used for data analysis. When there was no accumulation of tracer, the parameters of T_{max}, T_{min} and MS were not available. For subjects in whom T_{max}, T_{min} and MS were not available due to lack of tracer accumulation, we treated data as defect values in statistical analysis.

TABLE 1
Definitions of Functional Parameters in Salivary Gland Scintigraphy

Parameter	Definition
Uptake ratio	Gland-to-background ratio at the maximum count
T_{max}	Time at the maximum count (point B) (min)
T_{min}	Time interval from stimulation to minimum count (time interval between points C and D) (min)
Maximum accumulation	(b − a)/b × 100 (%)
Maximum secretion	(b − d)/b × 100 (%)

Labial Biopsy

The standard method was used to biopsy the minor salivary glands of the lower lip (*3*). The time interval between scintigraphy and biopsy was less than 3 mo, except for 1 patient for whom the time interval was 6 mo. After routine hematoxylin-eosin staining, the minor salivary gland tissue was histopathologically examined by an experienced pathologist. On the basis of standard grading criteria (*3*), histopathologic change was classified into a grade from 0 to 4 (Table 2).

Statistical Analysis

All values are expressed as mean ± SD. Statistical analysis was performed by using the Mann-Whitney *U* test or Spearman rank correlation test between groups. The Mann-Whitney *U* test was used for comparison of scintigraphic parameters between normal controls and Sjögren's syndrome. The Spearman rank correlation test was used for comparison between scintigraphic parameters and histopathologic grades. Values of $P < 0.05$ were considered statistically significant. Stepwise regression analysis was used to calculate an equation to correlate the histopathologic grade with the scintigraphic parameters.

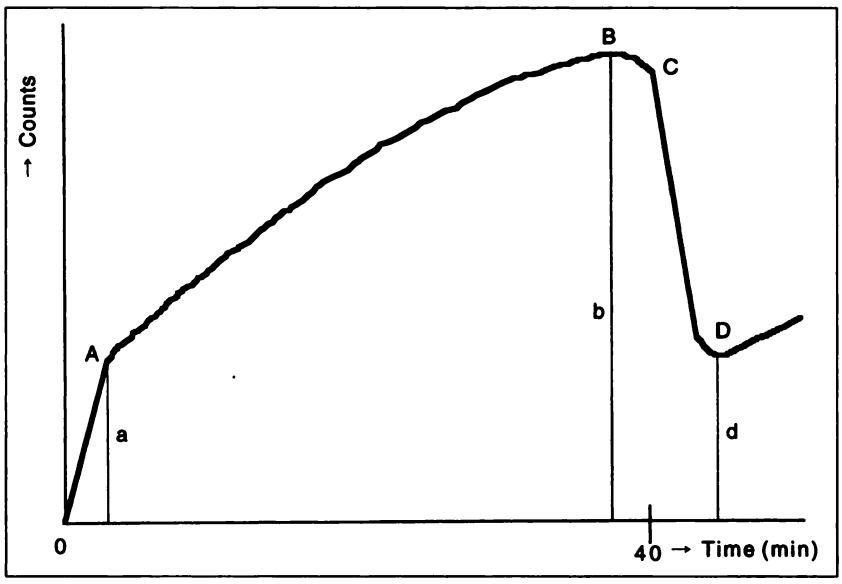

FIGURE 2. Schematic presentation of time-activity curve in salivary gland scintigraphy and definitions of points and parameters for data analysis. This represents a normal pattern.

TABLE 2
Histopathologic Grading Criteria of Labial Salivary Gland Biopsy

Grade	Lymphocytes per 4 mm² of salivary tissue
0	Absent
1	Slight infiltrate
2	Moderate infiltrate or less than one focus
3	One focus
4	More than one focus

Focus = an aggregate of 50 or more lymphocytes and histiocytes.

RESULTS

Comparison of Scintigraphic Parameters in Normal Controls and Sjögren's Syndrome

Comparison of scintigraphic parameters between normal controls and Sjögren's syndrome is summarized in Table 3. The UR of the parotid and submandibular glands significantly decreased in Sjögren's syndrome compared with normal controls ($P < 0.001$ and $P < 0.0001$, respectively) (Fig. 3A). The T_{min} of the parotid and submandibular glands increased significantly in Sjögren's syndrome compared with normal controls ($P < 0.05$ and $P < 0.05$, respectively) (Fig. 3B). The MA of the parotid and submandibular glands significantly decreased in Sjögren's syndrome compared with normal controls ($P < 0.01$ and $P < 0.001$, respectively) (Fig. 3C). The MS of the parotid and submandibular glands also significantly decreased in Sjögren's syndrome ($P < 0.0001$ and $P < 0.001$, respectively) (Fig. 3D). However, the T_{max} of the parotid and submandibular glands did not differ significantly between normal controls and Sjögren's syndrome. There were no statistically significant sex or age differences in the evaluation of salivary function by scintigraphy.

TABLE 3
Comparison of Scintigraphic Parameters in Normal Controls and Patients with Sjögren's Syndrome

Parameter	Gland	Group: Normal control (n = 12)	Group: Sjögren's syndrome (n = 39)	P
UR	Parotid	4.9 ± 1.2	2.9 ± 1.4	<0.001
	Submandibular	3.1 ± 0.5	1.8 ± 0.8	<0.0001
T_{max} (minutes)	Parotid	37.4 ± 3.2	35.5 ± 4.7	ns
	Submandibular	26.3 ± 7.4	22.5 ± 12.1	ns
T_{min} (minutes)	Parotid	2.4 ± 1.4	3.6 ± 1.9	<0.05
	Submandibular	2.9 ± 1.6	4.9 ± 2.6	<0.05
MA (%)	Parotid	78.1 ± 5.7	65.8 ± 16.4	<0.01
	Submandibular	62.4 ± 7.0	30.8 ± 25.1	<0.001
MS (%)	Parotid	76.8 ± 3.6	52.1 ± 19.1	<0.0001
	Submandibular	72.9 ± 6.3	51.8 ± 22.1	<0.001

Numbers are mean ± 1 SD.
UR = uptake ratio; ns = not significant; MA = maximum accumulation; MS = maximum secretion.

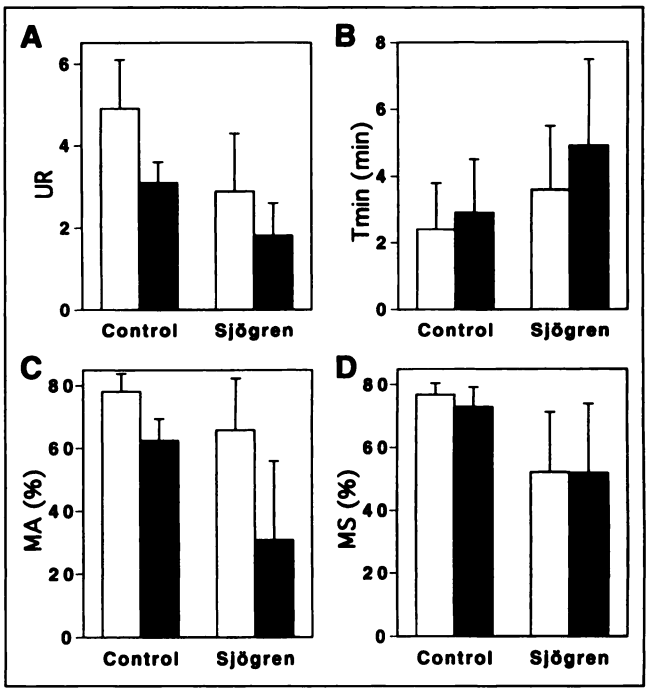

FIGURE 3. Comparison of normal controls and patients with Sjögren's syndrome for parotid (open bars) and submandibular glands (solid bars). (A) Uptake ratio (UR). (B) Time interval from stimulation to minimum count (T_{min}) (min). (C) Maximum accumulation (MA)(%). (D) Maximum secretion (MS)(%). Error bars represent 1 SD.

Correlation of Scintigraphic Parameters and Histopathologic Grades

Correlation of scintigraphic parameters and histopathologic grading is summarized in Table 4. The UR of the submandibular gland significantly decreased with the histopathologic grading ($P < 0.05$). The T_{min} of the parotid gland increased significantly with the histopathologic grading ($P < 0.05$) (Fig. 4A). The MA of the submandibular gland significantly decreased with the histopathologic grading ($P < 0.05$) (Fig. 4B). The T_{max} of the parotid gland increased with the histopathologic grading, although this was not statistically significant.

These data indicated that in the parotid gland the velocity of tracer secretion significantly decreased with the histopathologic grading. In the submandibular gland, the quantity of tracer accumulation significantly decreased with the histopathologic grading. Thus, decreased secretion velocity in the parotid gland and decreased accumulation in the submandibular gland were found to be sensitive indicators of salivary gland disease of Sjögren's syndrome.

By means of stepwise regression analysis, we calculated an equation to correlate the histopathologic grade with these scintigraphic parameters in patients with Sjögren's syndrome. All scintigraphic parameters were taken into account in the stepwise regression analysis. This statistically signifi-

TABLE 4
Correlation of Scintigraphic Parameters and Histopathologic Grading in Patients with Sjögren's Syndrome

Parameter	Gland	Histopathologic grade 1 (n = 13)	2 (n = 4)	3 (n = 8)	4 (n = 14)	P	r	No. of data
UR	Par	3.2 ± 1.2	2.8 ± 1.5	3.1 ± 2.1	2.5 ± 0.9	ns	−0.221	39
	Sub	2.0 ± 0.6	1.8 ± 1.0	1.8 ± 1.3	1.5 ± 0.5	<0.05	−0.340	39
T_{max} (minutes)	Par	33.8 ± 6.0	35.2 ± 4.4	36.6 ± 4.6	36.7 ± 3.2	ns	0.222	38
	Sub	22.1 ± 9.8	29.4 ± 14.8	21.1 ± 13.2	21.9 ± 13.8	ns	−0.027	37
T_{min} (minutes)	Par	2.9 ± 1.5	3.2 ± 1.2	2.9 ± 0.6	4.7 ± 2.4	<0.05	0.410	37
	Sub	4.2 ± 2.2	5.3 ± 2.8	4.9 ± 2.6	5.6 ± 3.1	ns	0.205	33
MA (%)	Par	68.5 ± 14.4	69.3 ± 12.9	60.0 ± 26.5	65.6 ± 12.0	ns	−0.113	39
	Sub	43.1 ± 23.7	37.2 ± 27.1	23.5 ± 29.5	21.6 ± 20.1	<0.05	−0.340	39
MS (%)	Par	57.4 ± 19.0	63.7 ± 9.1	41.6 ± 21.0	49.8 ± 18.2	ns	−0.227	38
	Sub	57.5 ± 12.7	49.3 ± 34.7	49.0 ± 24.1	48.6 ± 25.5	ns	−0.074	38

Numbers are mean ± 1 SD.
UR = uptake ratio; Par = parotid; ns = not significant; Sub = submandibular, MA = maximum accumulation; MS = maximum secretion.
No. of data = number of data available for each parameter.

cant correlation ($P < 0.05$) of the histopathologic grade and scintigraphic parameters was expressed using the following equation: Histopathologic grade = 2.304 − 0.014 × (submandibular MA) + 0.196 × (parotid T_{min}). The power of the equation (i.e., the R^2 value of the model) was found to be 0.588.

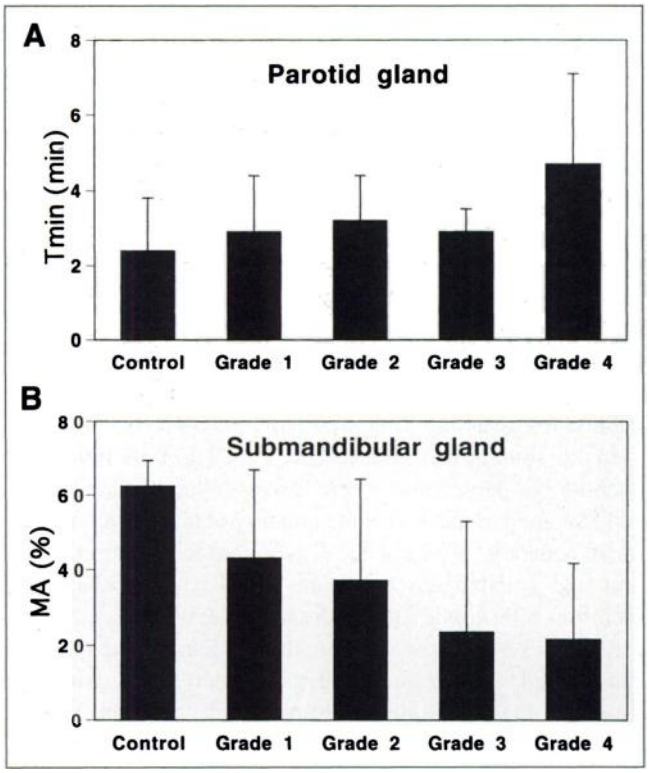

FIGURE 4. Comparison of normal controls and patients with Sjögren's syndrome of histopathologic grades 1 to 4. (A) Time interval from stimulation to minimum count (T_{min}) (min) for parotid gland. (B) Maximum accumulation (MA) (%) for submandibular gland. Error bars represent 1 SD.

Case Reports

Case 1. A 52-y-old woman complained of dry mouth and slightly dry eyes for 2 mo. Salivary gland scintigraphy showed good accumulation and good response to stimulation in all major salivary glands, although there was little spontaneous secretion (Fig. 5). The functional parameters were as follows: parotid UR = 4.4, submandibular UR = 3.1, parotid T_{max} = 39.0, submandibular T_{max} = 38.9, parotid

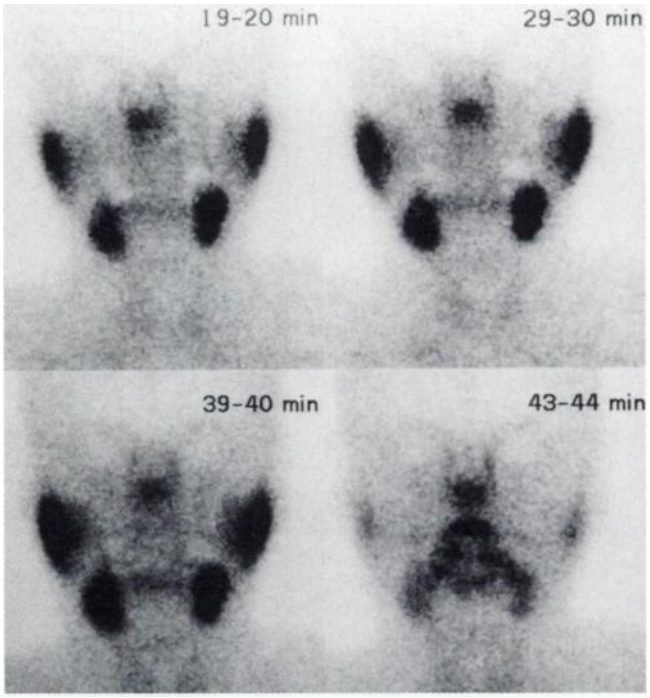

FIGURE 5. Case 1. Scintigrams of 52-y-old woman with Sjögren's syndrome (histopathologic grade 1) show good accumulation and good response to stimulation in both parotid and submandibular glands, although there was little spontaneous secretion.

T_{min} = 2.0, submandibular T_{min} = 2.3, parotid MA = 84.6, submandibular MA = 67.0, parotid MS = 74.1 and submandibular MS = 60.8. Labial biopsy revealed a histopathologic change of grade 1, and the patient was diagnosed as being in an early stage of Sjögren's syndrome.

Case 2. A 53-y-old woman complained of dry mouth and dry eyes for 3 mo. On salivary gland scintigrams, submandibular glands showed almost no accumulation of tracer (Fig. 6). The functional parameters were as follows: parotid UR = 4.6, submandibular UR = 1.2, parotid T_{max} = 39.2, submandibular T_{max} = 28.9, parotid T_{min} = 3.7, submandibular T_{min} = 5.7, parotid MA = 76.4, submandibular MA = 4.1, parotid MS = 62.7 and submandibular MS = 67.1. Labial biopsy revealed a histopathologic change of grade 3, and the patient was diagnosed as having Sjögren's syndrome.

Case 3. A 57-y-old woman had been suffering from dry mouth and dry eyes for 5 y. On salivary gland scintigrams, the parotid and submandibular glands showed almost no accumulation of tracer (Fig. 7). The functional parameters were as follows: parotid UR = 1.2, submandibular UR = 1.1, parotid T_{max} = 35.5, submandibular T_{max} = 6.3, parotid T_{min} = 9.2, submandibular T_{min} = 4.0, parotid MA = 41.9, submandibular MA = 6.9, parotid MS = 29.7 and submandibular MS = 74.8. Labial biopsy revealed a histopathologic change of grade 4, and the patient was diagnosed as having Sjögren's syndrome.

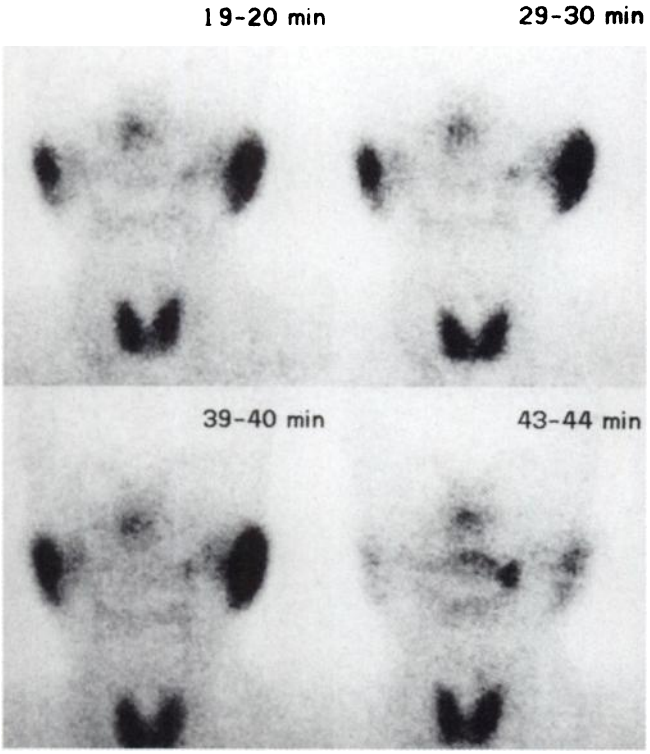

FIGURE 6. Case 2. Scintigrams of 53-y-old woman with Sjögren's syndrome (histopathologic grade 3) show almost no accumulation of tracer in submandibular glands.

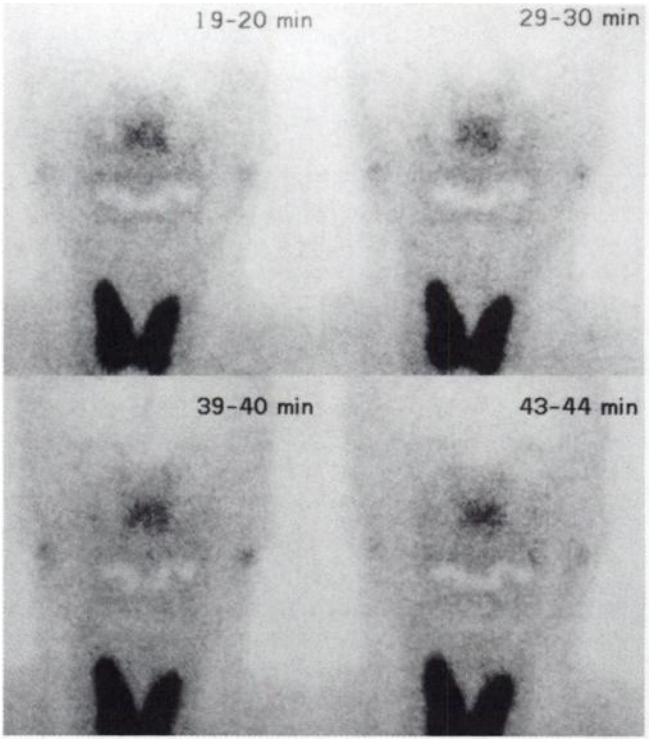

FIGURE 7. Case 3. Scintigrams of 57-y-old woman with Sjögren's syndrome (histopathologic grade 4) show almost no accumulation of tracer in parotid and submandibular glands.

DISCUSSION

Sjögren's syndrome is an autoimmune disease systematically affecting exocrine glands and other organs (*1,2*). Salivary glands are most frequently involved, and xerostomia is the most common symptom. However, subjective complaints of xerostomic patients do not necessarily reflect salivary gland disease. For evaluation of Sjögren's syndrome, a more objective and reliable method is necessary. Recently, salivary gland scintigraphy with ^{99m}Tc sodium pertechnetate has been used to evaluate salivary gland function in patients with Sjögren's syndrome (*4–13*). Although qualitative or quantitative scintigraphic studies have been attempted, there is still controversy about the optimal method for assessing Sjögren's syndrome (*4–13*).

In this study, we calculated UR, T_{max}, T_{min}, MA and MS as quantitative parameters of the salivary gland function. UR and MA are parameters for the quantity of accumulation, MS for the quantity of secretion, T_{max} for velocity of accumulation and spontaneous secretion and T_{min} for velocity of secretion after stimulation. The results have indicated that the UR and MA of the submandibular gland and the T_{min} of the parotid gland are significantly correlated with the histopathologic grading. Additionally, T_{max} of the parotid gland was also correlated with the histopathologic grading. Therefore, the data indicate that decreased secretion velocity in the parotid gland and decreased accumulation in the submandibular gland are highly sensitive indicators of salivary gland disease in Sjögren's syndrome.

It is not clear why the secretion velocity parameters in the parotid gland are more affected than accumulation parameters or why the accumulation parameters in the submandibular gland are more affected than velocity parameters. Differences in parenchymal volumes, spontaneous secretion and compositions of serous and mucous glands in the parotid and submandibular glands may provide a partial explanation. However, further investigation is necessary to clarify the different functional changes between the parotid and submandibular glands in patients with Sjögren's syndrome. In previous reports using qualitative and simpler quantitative analyses, Sugihara et al. (*9*) and Håkansson et al. (*11*) showed that the function of the submandibular gland was more affected than that of the parotid gland.

Several reports have described the relationship between salivary scintigraphic and histopathologic findings in Sjögren's syndrome (*4,5,7,13*), but none have dealt with quantitative scintigraphic parameters. Some reports have described qualitative scintigraphic findings that correlate with labial biopsy findings (*4,7,13*). However, Schall et al. (*5*) reported that there is no correlation of these findings. Although some reports have described the parameters of accumulation and secretion as valuable for diagnosing Sjögren's syndrome (*6,8,11,12*), there is no consensus as to which parameter is better for assessing salivary gland disease. These results indicate that decreased secretion velocity in the parotid gland and decreased accumulation in the submandibular gland are highly sensitive indicators of salivary gland disease in Sjögren's syndrome.

By means of a stepwise regression analysis, we have devised an equation to correlate the histopathologic grade with the two scintigraphic parameters, MA of the submandibular gland and T_{min} of the parotid gland. Thus, the histopathologic grade of patients with Sjögren's syndrome was correlated with these scintigraphic parameters. The results were found to be statistically significant. We believe that salivary gland scintigraphy is a most useful method to noninvasively evaluate salivary gland disease in patients with Sjögren's syndrome.

CONCLUSION

Salivary gland scintigraphy is an easy and noninvasive method for evaluating patients with Sjögren's syndrome. By using quantitative analysis, the secretion velocity in the parotid gland and accumulation in the submandibular gland were found to be highly sensitive parameters for evaluation of salivary gland disease in Sjögren's syndrome. The histopathologic grade was correlated with these scintigraphic parameters.

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