Sjögren's Syndrome: Comparison of Assessments with Quantitative Salivary Gland Scintigraphy and Contrast Sialography

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This study compared the quantitative parameters of salivary gland scintigraphy and the sialographic stages in patients with Sjögren's syndrome. **Methods:** One hundred sixteen patients suspected of having Sjögren's syndrome were examined with salivary gland scintigraphy and contrast sialography. When contrast sialography was used as the gold standard, Sjögren's syndrome was diagnosed in 50 of these 116 patients; Sjögren's syndrome was not seen in the other 66 patients. After injection of 370 MBq ^{99m}Tc-sodium pertechnetate, dynamic salivary gland scintigraphy with lemon juice stimulation was performed for 50 min. Functional parameters for the parotid and submandibular glands were calculated, and scintigraphic and sialographic results were compared. **Results:** With the progression of sialographic stages from 0 to 4, the quantity of tracer accumulation decreased in the submandibular gland ($P < 0.0001$), and the quantity of tracer secretion decreased in the parotid gland ($P < 0.0001$). The sialographic stage in patients with Sjögren's syndrome was correlated with these scintigraphic parameters ($P < 0.0001$): sialographic stage = $3.243 - 0.337 \times$ (submandibular gland uptake ratio) $- 0.026 \times$ (parotid gland maximum secretion). **Conclusion:** The decreased accumulation in the submandibular gland and the decreased secretion in the parotid gland were highly sensitive indicators of salivary gland disease in Sjögren's syndrome. The sialographic stage was correlated with these scintigraphic parameters.

Key Words: Sjögren's syndrome; salivary gland scintigraphy; sialography

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Sjögren's syndrome is an autoimmune disease that affects the salivary and lacrimal glands (*1,2*), and xerostomia is the most common oral symptom. In the diagnosis and evaluation of Sjögren's syndrome, an objective examination method is required, because the complaints of patients do not necessarily reflect the severity of their salivary gland disease. Although contrast sialography is widely used as the gold standard in the diagnosis of this syndrome, it is an invasive method that has several disadvantages and complications (*3–5*).

Recently, salivary gland scintigraphy with ^{99m}Tc-sodium pertechnetate has been used to evaluate salivary gland function in xerostomic patients (*6–15*). This scintigraphy is an easy and noninvasive method that is able to evaluate bilaterally both parotid and submandibular glands. To our knowledge, however, no standard method for assessing Sjögren's syndrome has been established. Furthermore, no report has dealt with the relationships between quantitative scintigraphic parameters and sialographic findings.

In this study we compared quantitative parameters of salivary gland scintigraphy and sialographic findings in Sjögren's syndrome. We determined useful scintigraphic parameters for evaluation of salivary gland disease and calculated an equation to correlate the sialographic stage with the scintigraphic parameters.

MATERIALS AND METHODS

Patients

The study at our institution involved 116 consecutive patients (105 women, 11 men; age range, 18–77 y; mean age, 54 y) who had xerostomia and were clinically suspected of having Sjögren's syndrome. All patients underwent both salivary gland scintigraphy and contrast sialography at our institution. When contrast sialography was used as the gold standard, Sjögren's syndrome was diagnosed in 50 of these 116 patients; Sjögren's syndrome was not seen in the other 66 patients. A definitive diagnosis in the 50 patients with Sjögren's syndrome was made after they had undergone complete physical examination and laboratory testing. The physical examination and laboratory testing included questionnaires for dry eye and dry mouth symptoms, Schirmer's I test, rose Bengal score, unstimulated and stimulated whole saliva collection, rheumatoid factors, antinuclear antibodies, and anti-Ro/SS-A and anti-La/SS-B antibodies. The 66 patients who did not have Sjögren's syndrome at contrast sialography had no evidence of Sjögren's syndrome at the physical examination and laboratory testing. Ultimately, no overt organic disease was found in the 66 patients, and the cause of their xerostomia remained undiagnosed. On the basis of contrast sialography, physical examination, and laboratory testing, they were determined not to have Sjögren's syndrome.

Of 50 patients with Sjögren's syndrome at contrast sialography,

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39 underwent labial salivary gland biopsy, and all these patients showed histopathologic changes of grade 1 or greater. Thus, there were no false-positive cases of contrast sialography in the 39 patients who underwent both contrast sialography and labial salivary gland biopsy. The 66 patients without Sjögren's syndrome at contrast sialography did not undergo labial salivary gland biopsy, because this technique is quite invasive.

Imaging Examinations

After intravenous injection of 370 MBq ^{99m}Tc-sodium pertechnetate, dynamic salivary gland scintigraphy was performed with a γ 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/frame for 50 min. Forty minutes after the injection, 2 mL lemon juice were administered intraorally as a stimulus.

All patients also underwent contrast sialography using a digital subtraction technique. Digital subtraction images were obtained with a 0.3-mm focal spot and a cesium iodide image-intensifying tube (Optiplanimat; Siemens, Erlangen, Germany) that operated at a voltage of 73 kV, a current of 28 mA, a total filtration equivalent to 3-mm aluminum, and a focus-subject distance of 115 cm. Images were obtained using a computed radiography system (Fuji Computed Radiography; Fuji Photo Film, Tokyo, Japan) and were displayed with a 1024 × 1024 matrix. A catheter was used to inject a 0.5- to 0.7-mL dose of iohexol (Omnipaque, 350 mg iodine/mL; Daiichi Seiyaku, Tokyo, Japan) into the Stensen's duct in patients. The images obtained before and after the injection of contrast material were then subtracted on the monitor of the computed radiography system. In cases of severe misregistration caused by patient motion, however, the subtraction was not performed, and only the images obtained after contrast material injection were used. The time interval between the scintigraphy and sialography was <3 mo.

Data Analysis

On all summation images of dynamic salivary gland scintigraphy, 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. A time–activity curve of each salivary gland was drawn using background subtraction and 3-point smoothing. In Figure 1, 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 min; and point D, the minimum count after stimulation (*16*). 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 were calculated for each salivary gland: uptake ratio (UR), T_{max}, T_{min}, maximum accumulation (MA), and maximum secretion (MS) (Table 1) (*16*). Mean values of the bilateral glands were used for data analysis. Where 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 because of lack of tracer accumulation, we treated their data as defect values in statistical analysis.

By using the method reported by Rubin and Holt (*17*), we classified contrast sialograms, according to the size of the contrast material collection, into 1 of the following 5 stages of salivary gland disease: stage 0 (normal), no contrast material collection (i.e., no evidence of Sjögren's syndrome); stage 1 (punctate), contrast material collection of 1 mm in diameter or smaller; stage 2 (globular), contrast material collection of 1–2 mm in diameter; stage 3 (cavitary), contrast material collection of 2 mm in diameter or larger; and stage 4 (destructive), complete destruction of the gland parenchyma. The size of contrast material collection was measured with a caliper on original images at contrast sialography.

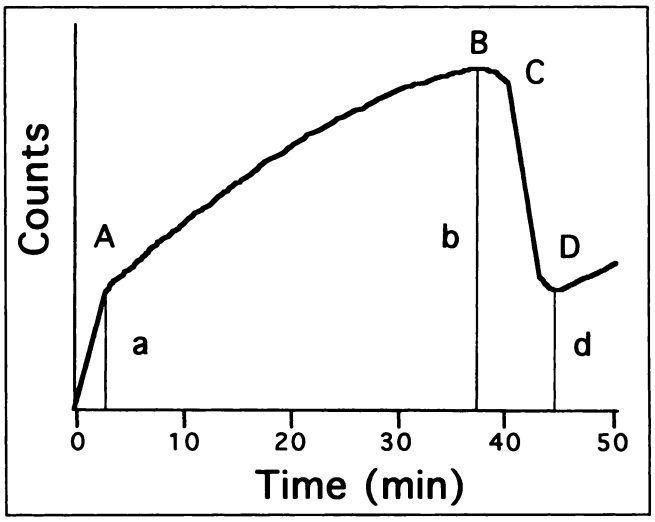

FIGURE 1. Schematic presentation of time–activity curve in salivary gland scintigraphy. This represents normal pattern.

A diagnosis of Sjögren's syndrome was made when the findings of contrast sialography showed stage 1 disease or greater (*17–19*). In this study, Sjögren's syndrome was diagnosed in 50 of the 116 patients, and Sjögren's syndrome was not seen in the other 66 patients.

Statistical Analysis

All values are expressed as mean ± SD. Statistical analysis was performed by using Mann–Whitney *U* test or Spearman rank correlation test between groups. The Mann–Whitney *U* test was used for comparison of scintigraphic parameters between healthy controls and Sjögren's syndrome. The Spearman rank correlation test was used for comparison between scintigraphic parameters and sialographic stages. $P < 0.05$ was considered statistically significant. Stepwise regression analysis was used to calculate an

TABLE 1
Definitions of Functional Parameters in Salivary Gland Scintigraphy

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

TABLE 2
Comparison of Scintigraphic Parameters in Healthy Volunteers and Patients with Sjögren's Syndrome

Parameter	Gland	Group: Healthy volunteer (n = 66)	Group: Sjögren's syndrome (n = 50)	P
UR	Parotid	4.7 ± 2.2	2.7 ± 1.3	<0.0001
	Submandibular	2.7 ± 1.1	1.5 ± 0.5	<0.0001
T_{max} (min)	Parotid	38.4 ± 5.6	35.6 ± 6.2	<0.05
	Submandibular	29.6 ± 11.2	21.7 ± 13.0	<0.001
T_{min} (min)	Parotid	3.8 ± 1.5	4.7 ± 2.2	<0.01
	Submandibular	3.9 ± 1.8	4.8 ± 2.4	<0.05
MA (%)	Parotid	80.0 ± 12.9	66.3 ± 14.9	<0.0001
	Submandibular	57.4 ± 18.1	26.5 ± 24.2	<0.0001
MS (%)	Parotid	74.5 ± 13.5	53.2 ± 21.1	<0.0001
	Submandibular	74.7 ± 17.9	66.0 ± 25.9	<0.05

Data are mean ± 1 SD.

equation to correlate the sialographic stage with the scintigraphic parameters.

RESULTS

Comparison of Scintigraphic Parameters in Healthy Volunteers and Sjögren's Syndrome

Comparison of scintigraphic parameters in healthy controls and Sjögren's syndrome is summarized in Table 2. The UR of the parotid and submandibular glands significantly decreased in Sjögren's syndrome as compared with healthy volunteers ($P < 0.0001$ and $P < 0.0001$, respectively). The T_{max} of the parotid and submandibular glands decreased significantly as compared with healthy volunteers ($P < 0.05$ and $P < 0.001$, respectively). The T_{min} of the parotid and submandibular glands increased significantly in Sjögren's syndrome compared with healthy volunteers ($P < 0.01$ and $P < 0.05$, respectively). The MA of the parotid and submandibular glands significantly decreased in Sjögren's syndrome compared with healthy volunteers ($P < 0.0001$ and $P < 0.0001$, respectively). The MS of the parotid and submandibular glands also significantly decreased in Sjögren's syndrome ($P < 0.0001$ and $P < 0.05$, respectively).

Additionally, there were no statistically significant sex and age differences in the evaluation of salivary function with scintigraphy.

Correlation of Scintigraphic Parameters and Sialographic Stages

The correlation of scintigraphic parameters and sialographic stages is summarized in Table 3. The UR of the parotid and submandibular glands significantly decreased with the sialographic staging ($P < 0.0001$ and $P < 0.0001$, respectively). The T_{max} of the parotid and submandibular glands decreased with the sialographic staging ($P < 0.001$ and $P < 0.001$, respectively). The T_{min} of the parotid and submandibular glands increased significantly with the sialographic staging ($P < 0.01$ and $P < 0.05$, respectively). The MA of the parotid and submandibular glands significantly decreased with the sialographic staging ($P < 0.0001$ and $P < 0.0001$, respectively). The MS of the parotid gland significantly decreased ($P < 0.0001$). The MS of the submandibular gland also decreased, although this was not statistically significant.

Regression analysis between scintigraphic parameters and sialographic stages was performed. In the submandibular gland, the decrease of the tracer accumulation highly correlated with the sialographic staging (UR: $r = -0.528$, $P < 0.0001$; MA: $r = -0.554$, $P < 0.0001$). In the parotid gland, the decrease of the tracer secretion highly correlated with the sialographic staging (MS: $r = -0.570$, $P < 0.0001$). Thus, decreased accumulation in the submandibular gland and decreased secretion in the parotid gland were highly sensitive indicators of salivary gland disease in Sjögren's syndrome.

TABLE 3
Correlation of Scintigraphic Parameters and Sialographic Staging in Patients with Sjögren's Syndrome

Parameter	Gland	Sialographic stage: 0 (n = 66)	1 (n = 18)	2 (n = 22)	3 (n = 8)	4 (n = 2)	P
UR	Par	4.7 ± 2.2	3.2 ± 1.1	2.6 ± 1.2	2.3 ± 1.6	1.4 ± 0.1	<0.0001
	Sub	2.7 ± 1.1	1.6 ± 0.5	1.6 ± 0.5	1.2 ± 0.1	1.1 ± 0.1	<0.0001
T_{max} (min)	Par	38.4 ± 5.6	38.0 ± 4.3	34.9 ± 7.0	31.5 ± 6.4	37.7 ± 2.4	<0.001
	Sub	29.6 ± 11.2	26.4 ± 12.4	20.6 ± 13.8	18.0 ± 9.4	7.0 ± 2.2	<0.001
T_{min} (min)	Par	3.8 ± 1.5	4.1 ± 2.2	4.5 ± 2.2	6.0 ± 1.6	7.5 ± 1.7	<0.01
	Sub	3.9 ± 1.8	4.3 ± 2.2	4.6 ± 2.3	5.5 ± 2.9	8.1 ± 2.0	<0.05
MA (%)	Par	80.0 ± 12.9	71.4 ± 13.5	64.3 ± 14.2	60.6 ± 19.0	64.7 ± 14.4	<0.0001
	Sub	57.4 ± 18.1	28.2 ± 24.4	27.6 ± 26.8	25.9 ± 18.5	5.1 ± 4.4	<0.0001
MS (%)	Par	74.5 ± 13.5	63.9 ± 12.2	47.0 ± 21.8	49.5 ± 27.9	37.3 ± 21.1	<0.0001
	Sub	74.7 ± 17.9	69.0 ± 21.5	66.1 ± 28.1	64.8 ± 32.5	43.4 ± 1.9	NS

Data are mean ± 1 SD.
Par = parotid; Sub = submandibular; NS = not significant.

By means of stepwise regression analysis, we calculated an equation to correlate the sialographic stage with these scintigraphic parameters in Sjögren's syndrome. This correlation ($P < 0.0001$) of the sialographic stage and scintigraphic parameters was expressed using the following equation: sialographic stage = 3.243 − 0.337 × (submandibular UR) − 0.026 × (parotid MS). The power of the equation (i.e., the r^2 value of the model) was 0.528.

Patient Presentations

Patient 1. A 31-y-old woman reported a slightly dry mouth for 2 mo. Salivary gland scintigraphy showed good accumulation and a good response to stimulation in both parotid and submandibular glands (Fig. 2). The functional parameters were as follows: parotid UR = 15, submandibular UR = 7.3; parotid T_{max} = 39.3, submandibular T_{max} = 39.8; parotid T_{min} = 1.8, submandibular T_{min} = 2.5; parotid MA = 79.7, submandibular MA = 78.8; parotid MS = 63.3, submandibular MS = 78.8. Contrast sialography showed a finding of stage 0, and the patient was not diagnosed with Sjögren's syndrome.

Patient 2. A 56-y-old woman had reported a dry mouth and dry eyes for 4 mo. On salivary gland scintigrams, the submandibular glands showed almost no accumulation of tracer and the parotid glands showed moderately decreased accumulation (Fig. 3). The functional parameters were as follows: parotid UR = 3.3, submandibular UR = 1.8; parotid T_{max} = 41.3, submandibular T_{max} = 9.1; parotid T_{min} = 9.1, submandibular T_{min} = 4.5; parotid MA = 56.2, submandibular MA = 4.1; parotid MS = 21.1, submandibular MS = 42.9. Contrast sialography showed a finding of stage 2, and the patient was diagnosed as having Sjögren's syndrome.

Patient 3. A 54-y-old woman had been suffering from dry mouth and dry eyes for 4 y. On salivary gland scintigrams, the parotid and submandibular glands showed almost no accumulation of tracer (Fig. 4). The functional parameters were as follows: parotid UR = 1.3, submandibular UR = 1.1; parotid T_{max} = 39.4, submandibular T_{max} = 8.5; parotid T_{min} = 6.4, submandibular T_{min} = 9.5; parotid MA = 74.9, submandibular MA = 2.0; parotid MS = 22.4, submandibular MS = 42.0. Contrast sialography showed a finding of stage 4, and the patient was diagnosed as having Sjögren's syndrome.

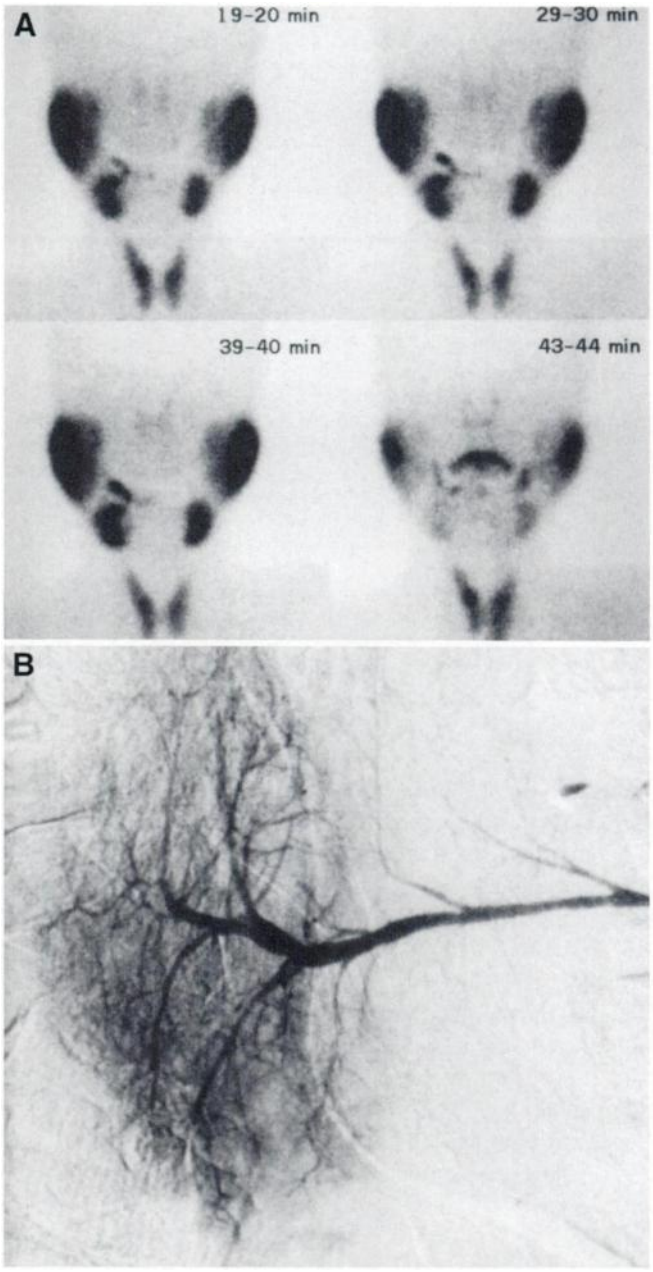

FIGURE 2. Images of 31-y-old woman (patient 1) without Sjögren's syndrome (sialographic stage 0). (A) Scintigrams show good accumulation and good response for stimulation in both parotid and submandibular glands. (B) Contrast sialogram in lateral view shows no contrast material collection (i.e., no evidence of Sjögren's syndrome).

DISCUSSION

Sjögren's syndrome is an autoimmune disease systematically affecting exocrine glands and other organs (*1,2*), and salivary glands are most frequently involved. Xerostomia is the most common symptom, but subjective complaints of xerostomic patients do not necessarily reflect salivary gland disease. Thus, for evaluation of Sjögren's syndrome, a more objective and reliable method is needed. Contrast sialography has been used as the gold standard in the diagnosis of Sjögren's syndrome (*6*). However, this is an invasive method in which an experienced clinician is required to cannulate the ducts; this is followed by a retrograde injection of a contrast material. The potential complications include failure of the cannulation procedure, duct trauma, painful overfilling of the gland, infection, and contrast material reactions (*3–5*).

Recently, salivary gland scintigraphy with ^{99m}Tc-sodium pertechnetate has been used in the noninvasive evaluation of salivary gland function in Sjögren's syndrome (*6–15*). However, there is still controversy about the optimal method

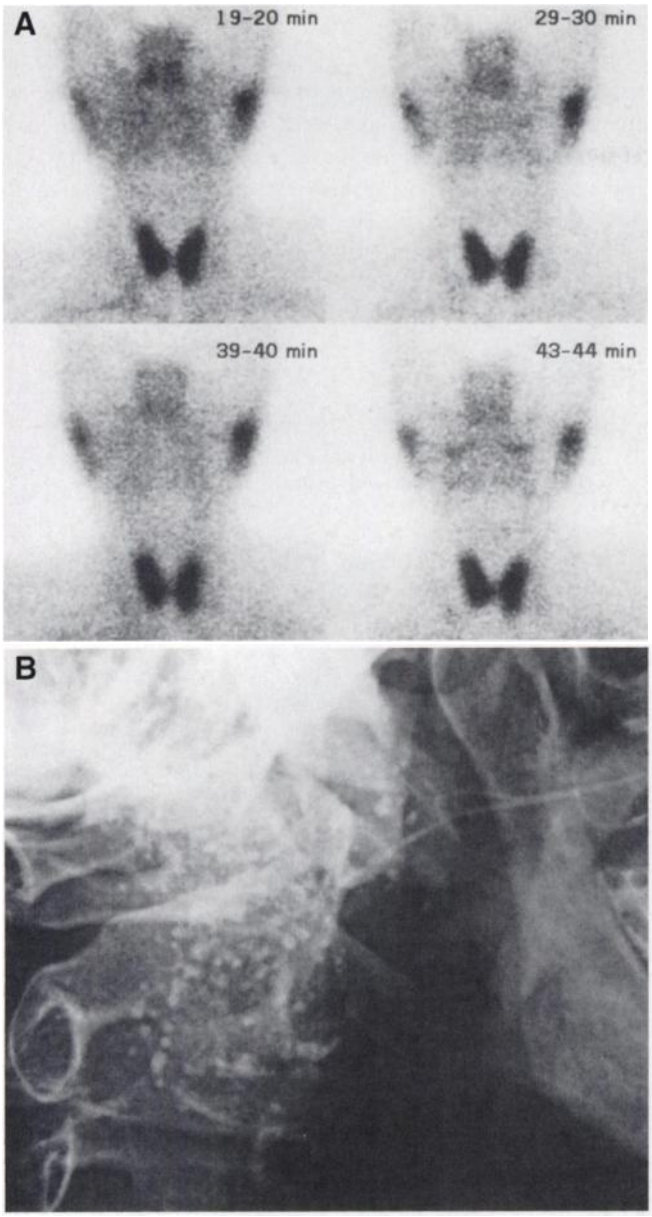

FIGURE 3. Images of 56-y-old woman (patient 2) with Sjögren's syndrome (sialographic stage 2). (A) Scintigrams show almost no accumulation of tracer in submandibular glands and moderately decreased accumulation in parotid glands. (B) Contrast sialogram in lateral view shows contrast material collections of 1–2 mm in diameter (stage 2).

for assessment of Sjögren's syndrome (*6–15*). Furthermore, no report has dealt with the relationships between quantitative scintigraphic parameters and contrast sialographic findings.

In this study, we calculated UR, T_{max}, T_{min}, MA, and MS as quantitative parameters of salivary gland function (*16*). 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. Our results indicate that the UR and MA of the submandibular gland and the MS of the parotid gland are highly correlated with the sialo-

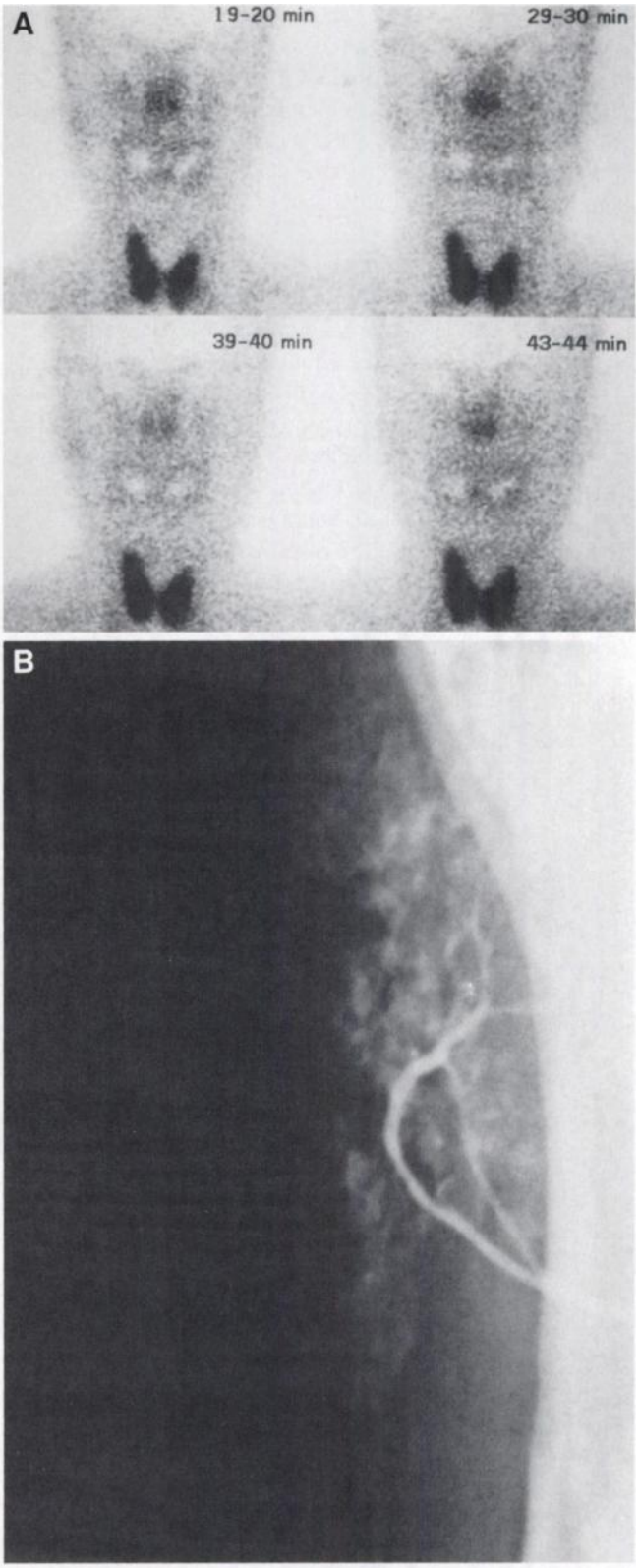

FIGURE 4. Images of 54-y-old woman (patient 3) with Sjögren's syndrome (sialographic stage 4). (A) Scintigrams show almost no accumulation of tracer in both parotid and submandibular glands. (B) Contrast sialogram in frontal view shows complete destruction of gland parenchyma (stage 4).

graphic staging. Therefore, the data indicate that decreased accumulation in the submandibular gland and decreased secretion in the parotid gland are highly sensitive indicators of salivary gland disease in Sjögren's syndrome. In our previous report, which compared scintigraphic parameters and histopathologic grades, we showed that decreased secretion velocity in the parotid gland and decreased accumulation in the submandibular gland were sensitive indicators of Sjögren's syndrome (*16*). Thus, both articles report that the accumulation parameters in the submandibular gland and secretion parameters in the parotid gland are sensitive parameters of Sjögren's syndrome.

It is not clear why the accumulation parameters in the submandibular gland are more affected than secretion parameters or why the secretion parameters in the parotid gland are more affected than accumulation parameters. In this regard, differences in parenchymal volumes, spontaneous secretion, and compositions of serous and mucous glands may provide a partial explanation for these functional changes (*16*). However, further study is needed to clarify the different functional changes between the parotid and submandibular glands in Sjögren's syndrome. In previous reports with qualitative and simpler quantitative analyses, Sugihara et al. (*11*) and Håkansson et al. (*13*) 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 sialographic findings in Sjögren's syndrome (*6,7,15*), but none of these has dealt with quantitative scintigraphic parameters. Some reports have described qualitative scintigraphic findings that correlate with sialographic findings (*6,15*). However, Schall et al. (*7*) report that there is no correlation between these findings. Although recent reports have described the parameters of accumulation and secretion as valuable for diagnosing Sjögren's syndrome (*8,10,13,14*), controversy remains as to which parameter is better for assessing salivary gland disease. Our results indicate that decreased accumulation in the submandibular gland and decreased secretion in the parotid 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 sialographic stage with the 2 scintigraphic parameters, UR of the submandibular gland and MS of the parotid gland. Thus, the sialographic stage of patients with Sjögren's syndrome was statistically significantly correlated with these scintigraphic parameters. We believe that salivary gland scintigraphy is a most useful method to noninvasively evaluate salivary gland disease in patients with Sjögren's syndrome.

CONCLUSION

In comparison with contrast sialography, salivary gland scintigraphy is an easy and noninvasive method for evaluation of patients with Sjögren's syndrome. Using quantitative analysis, the accumulation in the submandibular gland and secretion in the parotid gland were highly sensitive parameters for evaluation of salivary gland disease in Sjögren's syndrome. The sialographic stage was correlated with these scintigraphic parameters.

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