# Diagnostic Value of Salivary Gland Ultrasonographic Scoring System in Primary Sjögren's Syndrome: A Comparison with Scintigraphy and Biopsy

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***ABSTRACT.*** ***Objective.*** To compare an ultrasonographic (US) scoring system of salivary glands with scintigraphy and salivary gland biopsy, in order to evaluate its diagnostic value in primary Sjögren's syndrome (SS).

***Methods.*** In 135 patients with suspected SS, the grades of 5 US measures of both parotid and submandibular salivary glands were scored (0–48 scale). Diagnosis of primary SS was established following the American-European Consensus Group criteria of 2002. The patients' total scintigraphic score (0–12 scale) was determined and the histopathological changes of minor salivary glands graded. Area under the receiver-operating characteristic (ROC) curve was employed to evaluate the diagnostic value of the US scoring system.

***Results.*** Primary SS was diagnosed in 107 (79.2%) patients and the remaining 28 subjects (20.8%) constituted the control group. US changes of salivary glands were established in 98/107 patients with SS and in 14/28 controls. Mean US score was 26 in SS patients and 6 in controls. Through ROC curves, US arose as the best performer (0.95 ± 0.01), followed by scintigraphy (0.86 ± 0.31). Setting the cutoff score for US at 19 resulted in the best ratio of specificity (90.8%) to sensitivity (87.1%), while setting the cutoff scintigraphic score at 6 resulted in specificity of 86.1% and sensitivity of 67.1%. Among 70 patients with US score ≥ 19, a scintigraphic score > 6 was recorded in 54/70 (77.1%) and positive biopsy findings in 62/70 (88.5%) patients.

***Conclusion.*** We show high diagnostic accuracy of a novel US scoring system of salivary glands (0–48) in patients with primary SS comparable to invasive methods, i.e., scintigraphy and salivary gland biopsy. (First Release June 1 2009; J Rheumatol 2009;36:1495–500; doi:10.3899/jrheum.081267)

*Key Indexing Terms:*
SJÖGREN'S SYNDROME ULTRASONOGRAPHY SCINTIGRAPHY
SALIVARY GLANDS BIOPSY

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by lymphocytic infiltration and destruction of the salivary and lacrymal glands, leading to symptoms and signs of dry mouth and keratoconjunctivitis sicca[1]. The recently published classification criteria proposed by the American-European Consensus group (AECG) of 2002 include the unstimulated salivary flow test, sialography, and scintigraphy as methods for the assessment of salivary gland function[2]. The evaluation of salivary gland involvement in SS needs further improvement. Several studies have shown that parotid sialography was the most specific (92%–100%), while salivary gland scintigraphy was a very sensitive (83%) diagnostic method for primary SS[3-5]. However, sialography is an invasive procedure that could cause flares of glandular pain and swelling. Scintigraphy is a safe, but diagnostically nonspecific (63%) method, as abnormal findings can be found in patients with other diseases and in elderly subjects. In addition to standard tests for the assessment of salivary gland involvement in SS, new imaging techniques including computed tomography (CT)[6], magnetic resonance (MR)[7], and ultrasonography (US) of the salivary glands[6-10] have been studied. Among these, US of the major salivary glands seems the most attractive as a safe, noninvasive, non-irradiating, and inexpensive method. Recent studies have shown that US yields valuable information about the morphological changes of salivary glands in primary SS.

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In order to achieve good balance between sensitivity and specificity of this imaging approach, several semiquantitative US scoring systems have been developed[6,7,11]. The US scoring system of major salivary glands (0–48 scale) recently proposed by Hocevar, *et al*[12], based on the assessment of several US measures, may be an important advance in the diagnosis of primary SS.

The objective of our study was to evaluate the diagnostic value of this semiquantitative US scoring system (0–48) in assessment of oral involvement in primary SS, in comparison with the total scintigraphic score (0–12 scale) and other formal classification criteria for primary SS.

## MATERIALS AND METHODS

*Subjects*. The study included 135 consecutive subjects (128 women and 7 men, mean age 54.1, range 21–78 yrs) suspected to have primary SS and referred to the Institute of Rheumatology, which is a tertiary-care referral hospital in Belgrade. All subjects gave their informed consent to participate in the study. The Ethics Committee of the Institute of Rheumatology, Belgrade, Serbia, approved the study.

*Clinical and laboratory investigations*. Demographic features of subjects were collected. A questionnaire with 6 questions to assess both ocular and oral symptoms was given to each patient. Comorbidities and related treatment were recorded at the same time. All subjects quantified subjective feeling of ocular and oral dryness using the numerical visual analog scale (VAS; 0–10 scale). Objective xerophthalmia was assessed by Schirmer's I test and Rose-Bengal score determination. Oral involvement was evaluated by salivary scintigraphy and US examination of salivary glands. Histopathological investigation of the minor salivary glands, accepted as a "gold standard" in the diagnosis of primary SS, was performed in all subjects.

Serological tests included assessment of antinuclear antibodies (ANA) by indirect immunofluorescence on the Hep-2 cell line substrate (Orgentec Diagnostica, Mainz, Germany). The serum levels of rheumatoid factor (RF) were determined by laser nephelometry and anti-Ro/SSA and anti-La/SSB antibodies were tested by ELISA (Orgentec Diagnostica).

The patients were diagnosed with primary SS according to the AECG classification criteria of 2002[2].

*US of salivary glands*. US examination of the parotid and submandibular salivary glands was performed according to the method described by Hocevar, *et al*[12], simultaneously with the diagnostic procedures for primary SS. An experienced observer (VDM) with 8 years of experience of salivary gland US, who was blinded for clinical diagnosis, performed all US examinations, using a real-time, high-resolution ultrasound system (Voluson 730 Pro, General Electric, USA) equipped with a 4–10 MHz linear array transducer. Several US variables were investigated and the observed measures were assessed semiquantitatively in both paired glands for each subject: (1) Parenchymal echogeneity was evaluated in comparison with the thyroid gland parenchyma and the surrounding soft tissue (muscular structures, subcutaneous fat, etc.). If the echogeneity of salivary glands was isoechogenic to the thyroid, the grade was 0; if it was decreased, we graded it 1. (2) Parenchymal homogeneity was graded from 0 to 3, from homogenous parenchyma to grossly inhomogeneous gland (mild parenchymal inhomogeneity, grade 1, was treated as a normal finding). (3) The presence of hypoechogenic areas was graded from 0 to 3; (4) hyperechogenic reflections were graded from 0 to 3 in the parotid glands and from 0 (absent) to 1 (present) in the submandibular salivary glands; (5) clearness of salivary gland posterior borders was graded from 0 to 3. Finally, the US score was calculated by summation of the grades for the 5 measures described above of all 4 glands. US score thus ranged from 0 to 48.

*Scintigraphic measurements*. All subjects underwent salivary gland scintigraphy with radioactive technetium - $^{99m}$pertechnetate (99m) Tc-PT. The difference between the maximum and minimum excretion after stimulation using vitamin C divided by the maximum counts was defined as the excretion rate. According to this rate, a scoring system of 4 grades was applied: grade 3, severe dysfunction (excretion rate < 25%); grade 2, moderate dysfunction (25% ≤ excretion level < 40%); grade 1, mild dysfunction (40% ≤ excretion level < 50%); and grade 0, normal function (50% ≤ excretion level). The summation of the total scintigraphic score (0–12) of all 4 salivary glands was used as a semiquantitative index of total salivary gland function[13].

*Histopathological investigation*. Labial salivary gland (LSG) biopsy was performed in all subjects included in the study. The changes observed in 4 $mm^2$ of salivary gland tissue were scored from 0 to 4, according to the semiquantitative scoring method of Chisholm and Mason[14]. Grade 0 was given in the absence of inflammatory infiltrate, grade 1 for the presence of slight infiltrate, grade 2 for the presence of moderate infiltrate of focus score < 1 (focus score is defined as number of aggregates of ≥ 50 lymphocytes per 4 $mm^2$ of tissue). Grade 3 or 4 was assigned in the presence of focus score ≥ 1. Grade 3 and 4 were defined as pathological findings.

*Statistical analysis*. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 16.0; Student's t test, chi-squared test, and multivariate logistic regression analysis were employed. P values less than 0.05 were considered statistically significant. Discriminant validity was assessed by receiver-operating characteristic (ROC) curve analysis to compare the ability of US to discriminate between patients with primary SS and controls, in comparison with other formal classification criteria for primary SS. ROC curves were plotted to determine the area under the curve (AUC), which was used to evaluate the diagnostic performance of the test.

## RESULTS

*Subjects*. One hundred seven out of 135 subjects fulfilled the AECG classification criteria for primary SS (SS group). The remaining 28 subjects in whom SS was not confirmed constituted the control group (non-SS group). There was no statistically significant difference between these 2 groups in the mean age (54 vs 53 yrs, range 21–78, vs 30–76 yrs, respectively), male/female ratio (4/103 vs 3/25), use of anticholinergic drugs, and smoking.

The presence of clinically significant dry mouth and dry eye symptoms was confirmed by using numerical VAS ranging from 0 to 10. In patients with primary SS the average VAS score for dry eyes was 5.75 (range 0–10) and for dry mouth 6.60 (range 1–10). The patients with SS differed significantly for the duration of sicca symptoms ($p < 0.05$), objective features of dry eyes ($p < 0.05$) and dry mouth ($p < 0.05$), and for the presence of anti-Ro/SSA ($p < 0.01$) and/or anti-La/SSB antibodies ($p < 0.01$) compared to non-SS patients.

*Salivary scintigraphy and LSG biopsy*. The mean scintigraphic score in patients with SS was 10.4 (range 0–12) and 1.7 (0–8) in non-SS subjects. Normal scintigraphic finding (grade 0) was found in only 4 (3.7%) of 107 patients with SS and in 13 (46.4%) of 28 control subjects. There was a statistically significant difference in the mean scintigraphic scores between the patients with SS and non-SS controls ($p < 0.00$).

In the SS group, 6 (5.6%) patients had normal LSG biopsy findings (grade 0), while grade 1 was found in 18 patients

(16.9%), grade 2 in 13 patients (12.1%), grade 3 in 13 patients (12.1%), and grade 4 in 57 patients (53.3%). In the non-SS group, normal LSG biopsy finding (grade 0) was recorded in 17 patients (60.7%), grade 1 in 8 patients (28.6%), and grade 2 in 3 patients (10.7%). None of the non-SS subjects had grade 3 or grade 4 pathohistological findings indicative for primary SS.

*Diagnostic accuracy of US*. Structural changes of salivary glands visible on US were detected in 98/107 (91.6%) SS patients and in 14/28 (50.0%) subjects without confirmed SS. Patients with primary SS had significantly more frequent pathological findings of the posterior borders, parenchymal inhomogeneity with hypoechogenic areas and/or hyperechogenic reflections in salivary glands compared to non-SS subjects ($p < 0.01$). Mean US score in patients with SS was 26 (range 0–48) and 6 in the control group (0–14). In the population we studied the positive predictive value (PPV) for salivary gland US was 88.6% and the negative predictive value (NPV) was 87.7%. The PPV for sialoscintigraphy was 74.3% and the NPV was 72.3%. We used minor salivary gland biopsy as a gold standard to calculate the PPV and NPV for salivary gland US and scintigraphy in this cohort of patients.

ROC curves were employed to assess the diagnostic value of the proposed US scoring system for primary SS. We compared the accuracy of US and different valid diagnostic tests for primary SS (Figure 1). The area under the US ROC curve was significantly higher [0.95 ± 0.01; 95% confidence interval (CI) 0.91–0.98] in comparison to the area under the scintigraphy ROC curve (0.86 ± 0.31; 95% CI 0.80–0.92).

We set the US cutoff score as characteristic of primary SS at 19. This cutoff value represented the best sensitivity (87.1%) and specificity (90.8%) ratio as shown in Table 1.

Setting the scintigraphic cutoff score at 6 resulted in the sensitivity of 67.1% and specificity of 86.1% (Table 2).

In the SS group, 70 patients (65.4%) had US score ≥ 19, while 37 patients (34.6%) had US score < 19. Comparison of the clinical characteristics of SS patients with US scores ≥ 19 with those with US scores < 19 showed that they were of similar age (55.0 vs 54.8 yrs), but the patients with US score ≥ 19 had significantly longer average duration of the disease (5.9 vs 2.8 yrs; $p < 0.01$), and higher scintigraphic ($p < 0.01$) and salivary gland biopsy scores ($p < 0.01$). Among 70 patients (65.4%) with US score ≥ 19, a scintigraphic score > 6 and positive biopsy findings were recorded in 54/70 (77.1%) and 62/70 (88.6%) patients, respectively, while among 37 patients with US < 19 pathological scintigraphic score > 6 was recorded in 13/37 (35.1%) and positive biopsy findings in 8/37 (21.6%) patients. There was no statistically significant difference in the frequency of sicca symptoms, arthralgias, arthritis, Raynaud's phenomenon, lung fibrosis, neuropathy, or neuropsychiatric disorders, or in the prevalence of positive RF, ANA, anti-Ro/SSA, and anti-La/SSB antibodies. The group of patients with US score ≥ 19 had significantly higher concentrations of RF (189.5 IU/ml vs 104.2 IU/ml, respectively; $p < 0.01$).

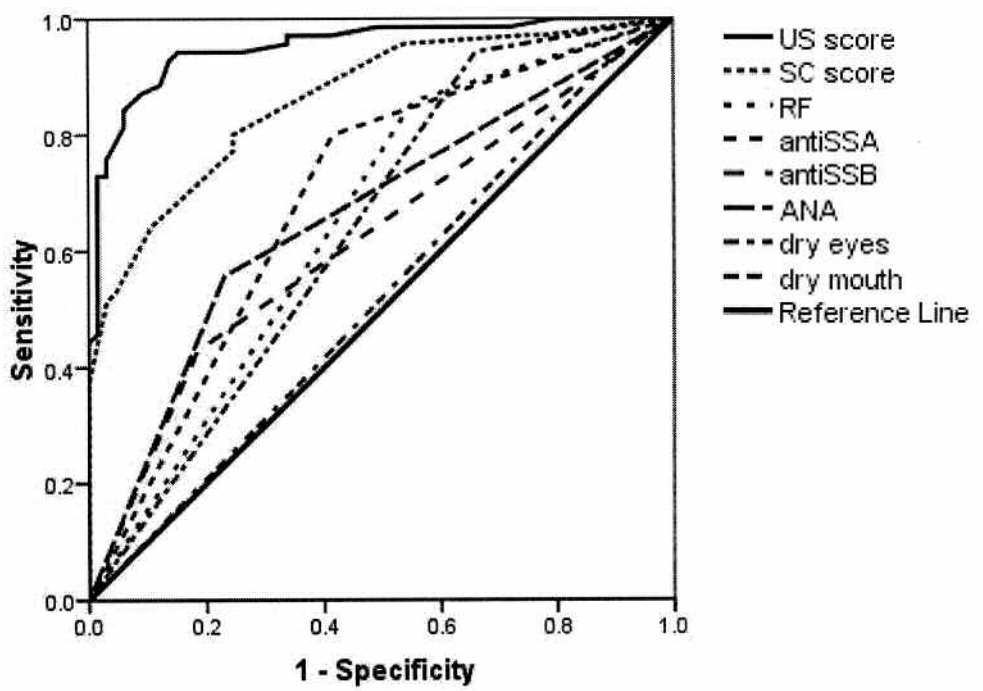


*Figure 1*. Receiver-operating characteristic (ROC) curves for the performance of salivary gland ultrasonography (US), scintigraphy (SC), and other diagnostic tests in discriminating between patients with primary Sjögren's syndrome and controls. Diagonal segments are produced by ties. RF: rheumatoid factor; ANA: antinuclear antibodies.

*Table 1*. Sensitivity and specificity of salivary gland US score (0–48 scale).

| Criterion | Sensitivity (%) | Specificity (%) |
|---|---|---|
| ≥ 0 | 100.00 | 0.00 |
| ≥ 1 | 100.00 | 7.70 |
| > 2 | 100.00 | 9.20 |
| > 3 | 100.00 | 10.80 |
| > 4 | 100.00 | 18.50 |
| > 5 | 100.00 | 20.00 |
| > 6 | 98.60 | 27.70 |
| > 7 | 98.60 | 32.30 |
| > 8 | 98.60 | 47.70 |
| > 9 | 98.60 | 56.80 |
| > 10 | 97.10 | 58.50 |
| > 11 | 97.10 | 61.50 |
| > 12 | 97.10 | 66.20 |
| > 13 | 95.70 | 66.20 |
| > 14 | 94.30 | 73.80 |
| > 15 | 94.30 | 80.00 |
| > 16 | 94.30 | 84.60 |
| > 17 | 92.90 | 86.20 |
| > 18 | 88.60 | 87.70 |
| > 19* | 87.10 | 90.80 |
| > 20 | 85.70 | 92.30 |
| > 21 | — | — |
| > 22 | 84.30 | 93.80 |
| > 23 | — | — |
| > 24 | 81.40 | 93.80 |
| > 25 | 78.60 | 95.40 |
| > 26 | 75.70 | 96.90 |
| > 27 | 72.90 | 96.90 |
| > 28 | 72.90 | 98.50 |
| > 29 | 68.60 | 98.50 |
| > 30 | 65.70 | 98.50 |
| > 31 | 60.00 | 98.50 |
| > 32 | 52.90 | 98.50 |
| > 33 | 50.00 | 98.50 |
| > 34 | 45.70 | 98.50 |
| > 35 | 44.30 | 100.00 |
| > 36 | 35.70 | 100.00 |
| > 37 | 32.90 | 100.00 |
| > 38 | 24.30 | 100.00 |
| > 39 | 21.40 | 100.00 |
| > 40 | 20.00 | 100.00 |
| > 41 | 15.70 | 100.00 |
| > 42 | 10.00 | 100.00 |
| > 43 | 8.60 | 100.00 |
| > 44 | 5.70 | 100.00 |
| > 45 | 2.90 | 100.00 |
| 47 | 1.40 | 100.00 |

AUC-ROC = 0.950, Standard error = 0.018. * Optimal cutoff point. US: ultrasonography; AUC-ROC: area under the receiver-operating characteristic curve.

*Table 2*. Sensitivity and specificity of salivary gland scintigraphy (0–12 scale).

| Criterion | Sensitivity (%) | Specificity (%) |
|---|---|---|
| ≥ 0 | 97.10 | 21.50 |
| > 1 | 97.10 | 24.60 |
| > 2 | 95.70 | 46.20 |
| > 3 | 94.30 | 49.20 |
| > 4 | 80.00 | 76.40 |
| > 5 | 77.10 | 75.40 |
| > 6* | 67.10 | 86.10 |
| > 7 | 64.30 | 89.20 |
| > 8 | 52.90 | 95.40 |
| > 9 | 51.40 | 96.90 |
| > 10 | 37.10 | 100.00 |
| > 11 | 34.30 | 100.00 |
| 12 | 0.00 | 100.00 |

AUC-ROC = 0.860, Standard error = 0.031. * Optimal cutoff point. AUC-ROC: area under the receiver-operating characteristic curve.

## DISCUSSION

Many different classification criteria have been proposed and used for the diagnosis of SS. The diagnostic approach in SS is rather complex and there is no single diagnostic test with satisfactory validity. LSG biopsy has been accepted as a gold standard in the diagnosis of SS due to its high specificity (91% to 94%) for the disease[4,14,15]. Current methods used in the evaluation of xerostomia including salivary scintigraphy, parotid sialography, and unstimulated salivary flow collection have limited sensitivity and specificity[4]. Salivary gland scintigraphy is a sensitive and valid method for evaluation of both parotid and submandibular gland function in patients with SS. Scintigraphy is preferred over parotid sialography, as an easy and less invasive method. Diminished salivary flow is in part functional and is not only caused by structural destruction of the salivary glands. No standard method for evaluation of salivary gland involvement in SS has been established. In this study, all patients had undergone a diagnostic labial salivary gland biopsy, which was used as a gold standard in the diagnosis of primary SS. All patients diagnosed with primary SS had either positive anti-Ro/SSA or anti-La/SSB antibodies or a focus score ≥ 1 in minor salivary gland biopsy to confirm the diagnosis. Pathologic scintigraphy results were found in 103 out of 107 (96.3%) patients with primary SS and they fulfilled the AECG criterion 5, which is related to the evaluation of salivary gland involvement. Four patients with negative scintigraphic results in the SS group had positive lip biopsy of either grade 3 or 4 and fulfilled 4 of the 6 items indicative of primary SS.

Twenty-eight patients (the non-SS group) did not fulfill the AECG criteria for primary SS, and all had negative lip biopsy results and were negative for anti-Ro/SSA and anti-La/SSB antibodies. Therefore, the fact that scintigraphy was the only diagnostic procedure to confirm salivary gland involvement has not significantly influenced the results presented in our study.

Noninvasive imaging techniques such as US, CT, and MR[6-11] are being studied and can be useful in the evaluation of oral involvement in primary SS. US of salivary glands is a simple and noninvasive method. The first studies of US abnormalities of salivary glands in patients with primary SS were published in the late 1980s and 1990s[6,8,9]. US has been

widely used in clinical practice, but there are different opinions about its value in the diagnosis of SS. Recently, color Doppler US has been used to evaluate the vascular anatomy and the pathological changes of the blood flow of the diseased salivary glands in patients with SS[11,16,17]. Several reports have shown that the sensitivity and specificity of salivary gland US ranged from 43% to 90% and from 84% to 100%, respectively[8,11,12,18-20]. These inconsistent results could be due to the application of different classification criteria sets for SS, different scoring systems for salivary gland morphological changes, employment of US scanning transducers with different resolutions, and inadequate objectivity in assessing US images.

In our study, we aimed to evaluate the diagnostic accuracy of the semiquantative US scoring system (0–48 scale) of major salivary glands recently proposed by Hocevar, *et al*[12] in comparison with salivary scintigraphy and other currently accepted formal classification criteria for primary SS including LSG biopsy.

Previous studies revealed that parenchymal inhomogeneity was the most important structural change of the salivary glands in patients with SS[8,10]. Our results show that parotid and submandibular salivary glands in patients with SS had advanced structural changes compared to patients with sicca syndrome without confirmed SS. In patients with primary SS, more frequent pathological changes of the posterior borders, parenchymal inhomogeneity with hypoechogenic areas, and/or hyperechogenic reflections in major salivary glands were observed. The mean US score in patients with primary SS of 26 (range 0–48) was significantly higher in comparison to the mean US score of 6 (0–14) in non-SS subjects. Considering the best sensitivity to specificity ratio, the US cutoff score characteristic for SS was set at 19. Among patients diagnosed with SS, 70 patients (65.4%) had US score ≥ 19, while 37 patients (34.6%) had US score < 19. In non-SS subjects, the highest US score was 14. Using 19 as the US cutoff score in this study, the diagnostic sensitivity for SS was 87.1% and specificity 90.8%. If higher scores were considered as positive, the specificity would have increased at the cost of lower sensitivity. In the original study by Hocevar, *et al*[12], the US cutoff score ≥ 17 characteristic of SS is close to our result. The cutoff scintigraphic score with the best sensitivity/specificity ratio was set at 6, with diagnostic sensitivity of 67.1% and specificity 86.1%. Our findings suggest that US changes of salivary glands are diagnostic for primary SS, which is in agreement with the recent report by Salaffi, *et al*[21], who recommend quantitative US assessment of salivary glands as a first-line imaging tool in the diagnosis of SS, better than scintigraphy.

By comparing SS patients with US score ≥ 19 with those with US score < 19 we found significantly longer average duration of the disease, higher RF concentrations, and more frequent positive scintigraphic and LSG biopsy scores in the former group. The frequency of clinical manifestations (dry eyes and mouth, arthralgia/arthritis, Raynaud's phenomenon, lung fibrosis, neuropsychiatric disorders) and the frequency of abnormal immunologic measures (RF, ANA, anti-Ro/SSA and anti-La/SSB antibodies) were similar between the groups.

Analysis of ROC curve was employed to evaluate the value of US score and other currently accepted methods in distinguishing the patients with primary SS from non-SS patients. A positive LSG histopathological result was the best performer, followed by salivary gland US and scintigraphy. According to Swets[22], salivary gland US is an excellent test regarding the diagnostic accuracy (area under US ROC curve is 0.95 ± 0.01), while the salivary gland scintigraphy is a good test (area under scintigraphic ROC curve is 0.86 ± 0.31). The AUC-ROC in all of these imaging investigations reached the range of good accuracy. Our findings are in agreement with other reports[10,12,18,20,21,23] that recommend the addition of salivary gland US to the AECG classification criteria for SS.

The results of our study support the notion that the US imaging of major salivary glands gives valuable objective evidence of salivary gland structural changes in patients suspected of having SS. In our opinion high-resolution salivary gland US as a noninvasive imaging procedure could be considered as another test of criterion 5 established by the AECG: salivary gland involvement, probably as an alternative method to sialography. In the case of patients with primary SS with advanced clinical symptoms and signs and positive autoantibodies (anti-Ro/SSA and/or anti-La/SSB), salivary US could be used as an alternative to lip biopsy to confirm the diagnosis.

Our study shows higher diagnostic value of the novel US scoring of salivary glands (0–48) in the evaluation of oral involvement in patients suspected of having primary SS compared to scintigraphy. Therefore, salivary gland US is a useful additional diagnostic tool for primary SS and suitable for patient followup. Future studies are necessary to define the US cutoff score with the best diagnostic accuracy.

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