Advances in salivary gland ultrasonography in primary Sjögren's syndrome

N. Luciano, F. Ferro, S. Bombardieri, C. Baldini

Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy.

Nicoletta Luciano, MD
Francesco Ferro, MD
Stefano Bombardieri, MD
Chiara Baldini, MD, PhD

Please address correspondence to:
Dr Chiara Baldini,
U.O. di Reumatologia,
Dipartimento di Medicina
Clinica e Sperimentale,
Università di Pisa,
via Roma 67,
56126 Pisa, Italy.
E-mail: chiara.baldini74@gmail.com

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ABSTRACT

Salivary gland ultrasonography (US) has recently been re-discovered as a useful tool to assess salivary gland involvement in primary Sjögren's syndrome (SS). In this review, we discuss US of the major salivary glands in the diagnosis of primary SS and analyse the possible added value of inclusion in classification criteria. We review the literature concerning associations between US of the major salivary glands, salivary gland histology and serology, with the possibility that US may be of value in disease stratification. We also examine the possible utility for US to monitor patient response to therapy in both clinical research and standard clinical care.

Introduction

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease, which typically involves major salivary and lachrymal glands (1, 2). Diagnosis remains challenging, but according to the international classification criteria a definitive diagnosis of primary SS is based on histologic demonstration of salivary and lachrymal inflammation and dysfunction in the context of a systemic abnormal immune response (3-6). In recent years, the use of salivary gland ultrasonography (US) has been increasingly performed to recognise glandular involvement in primary SS. Many studies have highlighted the diagnostic accuracy of this non-invasive, easily performed and feasible tool, and increasing evidence has recently suggested a potential role for patient stratification and monitoring over time (7-10). Therefore, although US of the major salivary glands was not included in the most recent classification criteria (11), it is possible, if not likely, that it could be introduced in both the diagnostic evaluation and monitoring of primary SS patients.

In this review, we summarise the evidence supporting the use of US of the major salivary glands for the diagnosis of primary SS, as well as the existing limitations that should be recognised to possibly introduce this tool into clinical trials and routine care. Moreover, we will evaluate critically whether US of the major salivary glands might be helpful in patients' stratification. Finally, we will discuss the controversial possibility of using US to monitor glandular response and damage accrual in primary SS patients.

US of the major salivary glands as a diagnostic tool for primary SS: where we stand and where we are heading

Salivary glands are key target organs in primary SS. Over time, several diagnostic techniques have been proposed to "characterise" their dysfunction and anatomical changes, with the aim of facilitating the diagnostic evaluation of primary SS. One of the earliest studies that documented the potential value of salivary ultrasonography in diagnosis of both primary SS and secondary SS was reported by De Vita *et al*. in 1992 (12). In this report, the authors proposed a grading based on the degree of salivary gland inhomogeneity for the diagnosis of primary SS. The results were encouraging and showed a sensitivity of 88.8% in primary SS and of 53.8% in secondary SS and a specificity of 84.6% and of 92.2% with respect to controls.

Many other reports have subsequently appeared concerning US of major salivary glands in primary SS diagnosis, comparing US with sialography, sialoscintigraphy and/or minor salivary gland biopsy (9, 12-29). Table I summarises some of the most relevant reported studies, specifically the scoring methods used for salivary gland US assessment and the inclusion criteria for the enrolment of subjects. In a recent

meta-analysis (30), Delli *et al*. examined the diagnostic properties of US of major salivary glands in diagnosing SS in comparison with the criteria applied in the classification of SS or in comparison with sialography, scintigraphy, sialometry, and histology of the salivary glands. The authors concluded a pooled sensitivity and specificity of 69% and 92%, respectively. Similarly, Song *et al*. (31) reported a pooled sensitivity and specificity of US of 77.4% (73.7–80.9) and 81.5% (77.6–85.0) compared to 80.0% (76.4–83.2) and 89.0% (85.8–91.8) of sialography in diagnosing SS when the gold standard were the international classification criteria for the disease.

In comparisons of US of major salivary gland and minor salivary gland biopsies, both Cornec (22) and Baldini *et al*. (27) found a fair correlation (r=0.61 and r=0.39, respectively) between US and the focus score (*i.e*. the number of mononuclear cell infiltrates containing at least 50 inflammatory cells in a 4 mm^2 glandular section) in primary SS patients with a diagnosis of ≤5 years. Astorri *et al*. (28) found that ultrasound had a positive predictive value of 85% and a striking negative predictive value of 96% compared to histology results. In 2017, Mossel *et al*. also reported a moderate association between parotid gland US and histology of parotid glands (r= =0.376) (29).

Most reports agree that inhomogeneity of the parenchyma is the most important sonographic feature of salivary gland involvement in primary SS (Figs. 1-2). More specifically, the number of hypoechoic or anechoic areas in each gland appeared to represent optimally the degree of the disruption of the salivary gland structure (13, 15, 20, 25, 32-36). Moreover, salivary gland inhomogeneity represents the most reliable feature to distinguish the disease from other pathological mimicker conditions (Table I) (15, 26, 37).

One finding that is more controversial in the identification of primary SS patients is glandular vascularity. Generally, a pattern of diffuse and scattered hypervascularity has been described as commonly detectable in primary SS. However, this pattern can be seen in other acute and chronic inflammatory diseases such as sarcoidosis and non-immune mediated sialoadenitis, and appears as non-specific (38). Carotti *et al*. in 2001 evaluated the changes in vascularity during the lemon juice stimulation test in 30 patients with primary SS in comparison with 30 controls suffering from dry mouth not due to primary SS. Based on the degree of chronic inflammatory changes at minor salivary gland biopsy, chronic sialadenitis (CS) was defined as mild in 10 and severe in 20 primary SS patients. The authors found that only the peak systolic velocity (PSV) and not the resistive index (RI) could be influenced by the degree of chronic inflammation seen in biopsies of minor salivary glands. The mean difference between the PSV values taken from parotids and submandibular glands before and during lemon juice stimulation was statistically significant (p=0.003 and p=0.01, respectively) in the controls. On the other hand, no significant changes in the PSV values were found in the whole group of primary SS patients. However, the changes in PSV values before and during lemon juice stimulation were statistically significant in both parotids (p=0.019) and submandibular glands (p=0.012), and not significantly different from those in the controls in primary SS patients with mild CS. The variability of RI taken from the salivary glands before and during lemon juice stimulation was not statistically significant in either primary SS patients or controls (39, 40).

Overall, the literature has pointed to the possibility to use US of the major salivary glands in the diagnostic evaluation of SS. However, the results also raise several issues that require clarification before recommending US of the major salivary glands in routine assessment of primary SS patients. First, standardisation of a US scoring system seems to be needed, characterised according to diagnostic accuracy for primary SS when compared to diseased and normal control subjects, as well as reliability. The suitability of US of the major salivary glands in diagnostic evaluation and possible classification criteria particularly with respect to biopsy, remains a subject of debate.

In 2012, therefore, an international group of experts was created with the aim of standardising the US procedure and creating a new US scoring system which could be universally used. Starting with a systematic review (41), this international group published an atlas on salivary gland ultrasound abnormalities in primary SS patients and listed the different echographic parameters to consider in routine practice. The parameters identified included echogenicity, homogeneity, number of hypo or anechoic areas, measure of the biggest hypo or anechoic area, location of the hypo-or anechoic area in the gland, number of lymph nodes in the glands, calcification, visibility of the posterior border, measure of the glands.

A trial exercise on inter- and intra-observer reliability was then conducted on static and real time images by some US trained experts: the highest levels of concordance were obtained for echogenicity and homogeneity of glandular parenchyma (37). Le Goff *et al*. (33) found in 290 suspected primary SS patients undergoing a standardised evaluation for primary SS, including US of the major salivary glands among the ACR/EULAR criteria, increased sensitivity from 87.4% to 91.1% when physician diagnosis was the reference standard. Similarly, Takagy *et al*. (42) recently demonstrated that an integrated score system of the ACR/EULAR and US classifications significantly improved the diagnostic value in patients with SS. In their study, the integrated ACR/EULAR and US score system accuracy was 91.9 and 93.0% for primary and secondary SS patients, respectively, over that by the ACR/EULAR criteria alone, which was 74.2 and 86.0%, respectively. At this time, considerable interest has been developed to include US of the salivary glands in classification criteria of primary SS. It appears likely that the "UTOPIA PROJECT: Integration of Salivary-Gland Ultrasonography in Classification Criteria for Primary Sjögren's Syndrome: an International Vignette-Based Study by Devauchelle *et al*. (33) will make it possible to include this promising tool in the diagnostic algorithm for primary SS patients.

Table I. Relevant studies of the literature assessing SGUS diagnostic accuracy in pSS: scoring items.

Authors	Year	Patients	Scoring items and range
De Vita S. *et al*. (9)	1992	27 pSS, 26 sSS, 26 symptomatic ctrl, 64 HV	Parenchymal inhomogeneity: normal, mild, evident, gross (range: 0-6, cut-off>1)
Salaffi F. *et al*. (10)	2000	30 pSS, 30 symptomatic ctrl	Parenchymal inhomogeneity: normal , mild, moderate, evident, gross (range: 0-16)
Niemela R.K. *et al*. (11)	2004	27 pSS, 27 symptomatic ctrl, 27 HV	Parenchymal inhomogeneity , hyperechoic bands, size of the gland, hypo- anechoic lesions
Hocevar A. *et al*. (12)	2005	68 pSS, 150 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, number of hypoechoic lesions, hyperechogenic reflections, visibility of the posterior borders (range: 0-48, cut-off ≥17)
Wernicke D. *et al*. (13)	2008	57 pSS, 33 sSS, 78 symptomatic ctrl, 148 HV	Parenchymal inhomogeneity: normal, mild, evident
Salaffi F. *et al*. (14)	2008	77 pSS, 79 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, size of the glands, visibility of the posterior borders (range: 0-16)
Takagi Y. *et al*. (15)	2010	188 pSS , 172 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, number of hypoechoic lesions, hyperechogenic reflections, visibility of the posterior borders
Milic V. *et al*. (16)	2009	107 pSS, 28 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, number of hypoechoic lesions, hyperechogenic reflections, visibility of the posterior borders (range 0-48, cut-off ≥19)
Milic V *et al*. (17)	2010	115 pSS, 44sSS, 50 symptomatic ctrl, 36 HV	Parenchymal echogenicity, inhomogeneity, size of the glands, focal changes, visibility of the posterior borders (range: 0-12, cut-off ≥6)
Milic V. *et al*. (18)	2012	140 pSS, 50 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, size of the glands, visibility of the posterior borders (range: 0-16, cut-off ≥7)
Cornec D. *et al*. (19)	2013	78 pSS, 16 sSS, 64 symptomatic ctrl	hypoechogenic areas and hyperechogenic bands (range: 0-16, cut-off≥2 in each gland)
Cornec D. *et al*. (20)	2014	45 pSS, 56 symptomatic ctrl	hypoechogenic areas and hyperechogenic bands (range: 0-16, cut-off≥2 in each gland)
Theander E. *et al*. (21)	2014	105 pSS, 57 symptomatic ctrl	Parenchymal inhomogeneity (range 0-3, cut-off≥2 considering the highest score among 4 glands)
Hammenfors D. *et al*. (22)	2015	97 pSS	Parenchymal inhomogeneity (range 0-3, cut-off≥2 considering the highest score among 4 glands)
Luciano N. *et al*. (23)	2015	55 pSS, 54 UCTD	Parenchymal echogenicity, inhomogeneity, size of the glands, visibility of the posterior borders (range: 0-6, cut-off>1)
Baldini C. *et al*. (24)	2015	50 pSS, 57 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, size of the glands, visibility of the posterior borders (range: 0-6, cut-off>1)
Astorri E. *et al*. (25)	2016	36 pSS, 49 symptomatic ctrl	Parenchymal echogenicity, inhomogeneity, size of the glands, visibility of the posterior borders
Mossel E. *et al*. (26)	2017	103 suspected pSS	Parenchymal echogenicity, inhomogeneity, number of hypoechoic lesions, hyperechogenic reflections, visibility of the posterior borders (range: 0-48, cut-off ≥15)

US of the major salivary glands for the identification of primary SS different subsets: where we stand and where we are heading

Salivary gland enlargement is a typical primary SS manifestation, detected in almost one third of primary SS patients and considered as a risk factor for poor prognosis including lymphoproliferative complications (43-45). US of major salivary glands in primary SS has made it possible to identify a subgroup of patients with subclinical involvement of major salivary glands, with no clinically evident salivary gland enlargement. In other words, some primary SS patients apparently present abnormal findings at US without an overt enlargement of their glands. On the other hand, other patients present normal glands at the US and, according to Devauchelle *et al*. (46), do not present any change in their sonographic pattern over time. Several authors, have then, tried to explore whether patients with pathological US findings may have different characteristics with respect to those with normal US examination.

Hammenfors *et al*. described a significant correlation between pathological US findings and focal chronic inflammation of the minor salivary glands (r=0.219, p=0.05) in 97 primary SS patients; in addition, they also showed a good association between a much higher US score and subjective sicca symptoms r=0.549, p<0.001). Finally, the authors found a significant association between anti-Ro/SSA antibodies posi-

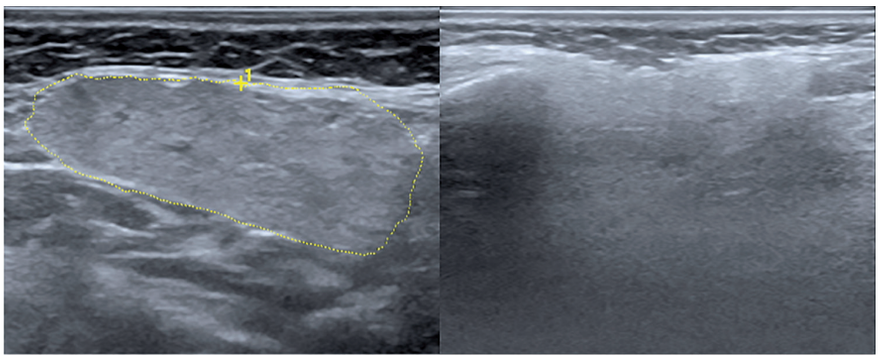

Fig. 1. Normal submandibular (on the left) and parotid (on the right) glands.

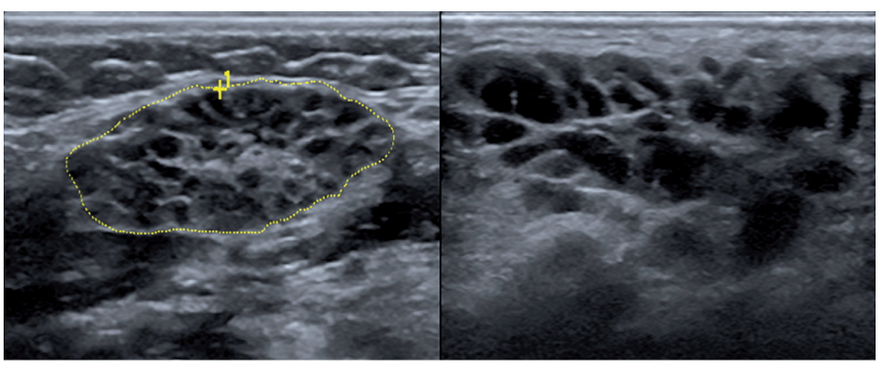

Fig. 2. A submandibular (on the left) and a parotid (on the right) gland with inhomogeneous parenchyma characterised by numerous and diffuse anechoic areas.

tivity and US abnormalities. Specifically, anti-Ro/SSA were elevated in 41/50 patients with US pathology compared to 23/46 patients with normal appearing major salivary glands (p<0.001) (25). Similarly, Fidelix *et al*. (47) observed in a cohort of 70 patients with primary SS that abnormal US findings correlated with lower salivary flow, positivity of autoantibodies (antinuclear antibodies, anti-Ro/SSA and anti-La/SSB antibodies, rheumatoid factor), higher IgG levels and an ESSDAI value >5. Intriguingly, Theander *et al*. (24) correlated higher US scores with disease-specific autoantibodies, high levels of IgG and some lymphoma risk markers such as salivary gland swelling, skin vasculitis, germinal center-like structures in salivary gland biopsy findings, and $CD4^+$ T cell lymphopenia, suggesting that US may help to identify SS at risk of lymphoma. From this perspective, not only clearly evident salivary gland enlargement but also subclinical abnormalities in the major salivary glands may represent additional risk factors for lymphoma development in primary SS.

Information concerning not only the presence of hypoechoic areas in the glands but also indirect signs of fibrosis and damage on ultrasound may also provide indirect information on salivary gland functional impairment. Martini *et al*. (48) suggested that a pathological US score in submandibular glands closely correlated with both salivary flow impairment and a decrease of salivary cystatin S, an indirect biomarker of salivary gland hypofunction. Nonetheless, further description and clinical correlations are needed to better characterise use of US to measure glandular damage and damage accrual.

Dejaco *et al*. (49) performed US and real-time tissue elastography (RTS) in 45 primary SS patients, 24 sicca patients and 11 healthy controls. The authors observed that in cases with an inconclusive B-mode ultrasonography result, RTS led to a sensitive (66.7%) and specific (85.7%) classification of patients and sicca controls. RTS, but not B-mode ultrasonography, reflected impaired salivary gland function according to the Saxon test (50) and was associated with sialo-scintigraphy scores. Various sonoelastographic modalities, including real-time tissue elastography, Virtual Touch imaging and quantification have provided promising results. Hofauer *et al*. demonstrated that glandular stiffness, measured by Virtual Touch quantification, was significantly higher in 50 patients with SS than in patients with sicca symptoms. Specifically, In Virtual Touch quantification, values for parotid (mean: 2.99 m/s) and submandibular glands (mean: 2.54 m/s) in the SS group were higher than those for parotid (mean: 2.16 m/s) and submandibular (mean: 2.04 m/s) glands in the control group (p=0.001 and p=5 0.008) (51). Moreover, Kimura-Hayama *et al*. compared elastography ultrasound with B-mode and several salivary inflammatory and pro-fibrotic chemokines and suggested that an increased shear wave velocity might represent chronic glandular inflammation rather than fibrotic changes. The ongoing multicentre HarmonicSS project (*i.e*. HARMONIzation and integrative analysis of regional, national and international Cohorts on primary Sjögren's Syndrome towards improved stratification, treatment and health policy making http://harmonicss.eu/) will specifically explore the possibility of assessing primary SS-related glandular damage by using salivary gland ultrasonography in primary SS.

US of the major salivary glands for the monitoring of therapeutic response in primary SS: where we stand and where we are heading

Given its non-invasive nature, US of major salivary glands seems to be the ideal tool to monitor salivary gland changes over time, especially now that novel biologic agents are available (52-54). Jousse-Joulin *et al*. (55) evaluated changes in salivary gland echostructure and vascularisation after rituximab treatment in 28 patients with primary SS enrolled in the multicenter, randomised, double-blind, placebo-controlled Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome (TEARS) trial undergoing salivary gland ultrasonography before the first placebo or rituximab infusion and then 6 months later. US of both parotid and submandibular glands was performed using a semiquantitative score

of 0–4, with improvement defined as a ≥1-point decrease. The authors also evaluated the size of each gland, and vascularisation based on the resistive index of the transverse facial artery of the parotid gland before and after lemon juice stimulation. Parotid parenchyma echostructure was improved in 50% of rituximab-treated versus 7% of placebo-treated patients. In the submandibular glands, echostructure also was improved in a 36% of rituximab-treated *versus* 7% of placebo-treated patients, although the difference was not statistically significant. Gland sizes and resistive index remained unchanged. In the same study, Cornec *et al*. (56) found that the highest US grade in patients with primary SS was associated with the absence of a response to a single rituximab course after 6 months. Similarly, Fisher *et al*. (57) compared the effects of rituximab *versus* placebo on US in primary SS in a multicentre, multiobserver phase III trial sub study of 52 subjects (n=26 rituximab and n=26 placebo). A 0-11 score (TUS) comprising domains of echogenicity, homogeneity, glandular definition, glands involved, and hypoechoic foci size was assigned at baseline, and weeks 16 and 48. The authors demonstrated a significant improvement of the TUS after rituximab versus placebo only in visibility of the salivary gland posterior border, while no improvement was seen for any of the other parameters (58). It was disappointing that no changes were observed in the vast majority of patients in the hypoechogenic areas, which are considered the US hallmark of primary SS. This finding has been explained in different ways: the corresponding histopathological lesions of the hypoechoic areas measured by ultrasound remain unknown (*i.e*. inflammation, damage or both). Perhaps integrating US, salivary gland MRI and histology may provide useful information to better distinguish reversible from irreversible findings at US. Moreover, the sensitivity to change of the US of major salivary glands should be determined in longer clinical trials. Nonetheless, US of major salivary glands in primary SS has opened new possibilities for diagnosis and monitoring, and further studies should provide the capacity to better exploit possible advantages of this technique.

Conclusions

In conclusion, a critical reappraisal of US of major salivary glands has provided important information on the potential usefulness and limitations of this tool for the diagnosis and the prognostic evaluation of primary SS patients. A general consensus is that the inclusion of US in classification criteria for the disease might improve diagnostic accuracy. Uncertainties may remain concerning the prognostic value and role in monitoring therapeutic response of salivary ultrasound. Hopefully, further research will provide knowledge concerning how to use US in primary SS to its optimal value, not only for research, but also for diagnosis and management of individual patients in routine clinical care.

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