Sonoelastography of salivary glands for diagnosis and clinical evaluation in primary Sjögren's syndrome

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Received on June 29, 2021; accepted in revised form on October 4, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 133): S184-S189.

Key words: Sjögren's syndrome, salivary glands, sonoelastography, diagnosis

Funding: this work was supported by Peking University People's Hospital Research and Development Funds (RS2020-01), the National Science Foundation of China (no. 81601417 and 81801618) and the Clinical Medicine Plus X-Young Scholars Project of Peking University (PKU2021LCXQ008).

Competing interests: none declared.

ABSTRACT

Objective. *To explore the performance of sonoelastography (SE) in diagnosis and clinical evaluation of primary Sjögren's syndrome (pSS).*

Methods. *SE examination of major salivary glands was conducted for 79 pSS patients, 39 disease controls and 15 healthy subjects. Elastographic images were determined with a qualitative 4-point scoring method. Receiver operating characteristic (ROC) curve was employed to evaluate the performance of the elasticity scoring method and the best cut-off value was determined. The associations between elasticity scores and disease characteristics were analysed to evaluate the clinical value of SE for pSS.*

Results. *Elasticity scores of parotid and submandibular glands in pSS group were significantly higher than those in the non-pSS group ($p<0.001$). The sum of the scores of all four glands provided the largest AUC-ROC (0.916, 95% CI 0.87–0.962), compared with that of bilateral parotid glands (0.857, 95% CI 0.794–0.919) and that of bilateral submandibular glands (0.783, 95% CI 0.704–0.863). The optimal cut-off value was 9 for combined evaluation of all four glands (81% sensitivity and 87% specificity, respectively). The elasticity scores of parotid glands in patients with disease duration >10 years experienced significant difference as compared to patients with disease duration ≤5 years and 5-10 years respectively ($p=0.007$, 0.009, respectively), whereas it presented no variations between the disease duration ≤5 years and 5–10 years ($p=0.952$).*

Conclusion. *Sonoelastography, performed simultaneously with ultrasonography, is an additional tool for the assessment of the salivary glands in patients with pSS. The elasticity is closely associated with disease duration.*

Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease clinically characterised by xerophthalmia and xerostomia (1). Histophathological examination shows lymphocytic infiltration and destruction of the exocrine glands, including salivary and lachrymal glands (2, 3). Accurate assessment of salivary gland involvement contributes significantly to the diagnosis of primary Sjögren's syndrome (pSS). Currently, there have existed various imaging techniques in assessing the involvement of salivary glands for patients with SS, such as sialoscintigraphy, sialography, MRI, CT and biopsy. However, considering that these techniques are mostly invasive and costly and can lead to irradiation, they are still not widely used in daily clinical practice. Ultrasonography (US), as a convenient and non-invasive technique, has been demonstrated to improve diagnostic accuracy in the assessment of salivary gland involvement for pSS (3-6).

Sonoelastography (SE), on the other hand, is a rapidly developing technique by which the tissue elasticity or stiffness property can be measured (7). It provides information on parenchymal elasticity by colour scale coding the different degrees of mechanical-elastic deformation. This information is collected by using the normal ultrasound probe and applying a vertical compression to the tissues manually or automatically (8). The tissues undergo varying degrees of deformation in relation to their stiffness. The elastogram displaying the resultant elasticity data is depicted by a qualitative scoring method. Stiffer lesions are assigned higher elasticity scores. SE has been investigated in the differential diagnosis of focal nodule of breast, thyroid, prostate and salivary gland and liver fibrosis where sound evidence indicates it as an accurate and reproducible method (8-12). When us-

ing strain ratio or virtual acoustic radiation force impulse imaging (ARFI) method, SE has been previously studied in some small sample studies demonstrating abnormalities of patients with pSS compared with heathy controls (13-17). However, there are yet few data supporting the diagnostic accuracy of this technique in distinguishing SS from other rheumatic diseases that may mimic SS (18, 19). Moreover, it is unclear whether SE is related to the clinical parameters in pSS.

The present study was aimed to explore the performance of SE in the diagnosis of pSS using a qualitative elasticity scoring method and evaluate the association between elasticity and disease characteristics.

Materials and methods

Study population

The study was conducted in a cohort of 79 patients with pSS enrolled between March 2019 and March 2021, who fulfilled the American-European Consensus Group (AECG) or American College of Rheumatology (ACR) criteria (20, 21). The control group included 39 patients with SS related manifestation but without SS and 15 healthy subjects. The study was approved by the medical ethics committee of the Institute of Peking University, all the participants provided written consent, and the study was performed according to the guidelines of the Declaration of Helsinki.

Clinical assessment and serological tests

All patients underwent a diagnostic work-up for pSS, and disease activity was assessed. The questionnaire-based evaluation included the following: (1) ocular symptoms; (2) oral symptoms; (3) ocular signs (Schirmer I test <5 mm in 5 minutes, ocular staining score >4 according to the van Bijsterveld scoring system); (4) salivary gland involvement as determined using parotid sialography and salivary scintigraphy; (5) positive results on histopathological examination of biopsy specimen of minor small labial glands (MSGs); (6) serological tests including those for anti-SSA, anti-SSB, antinuclear antibody (ANA), rheumatoid factor (RF), and immune globulins (IgG, IgA, IgM, and γ-globulin%); (7) and other systemic manifestations such as purpura, arthritis and renal tubular acidosis. In order to further explore the significance of the sonoelastographic scores in different stages of pSS, we classified the pSS patients into 3 groups according to symptom duration [disease duration≤5 years (n=49), 5-10 years (n=17), >10 years (n=13)].

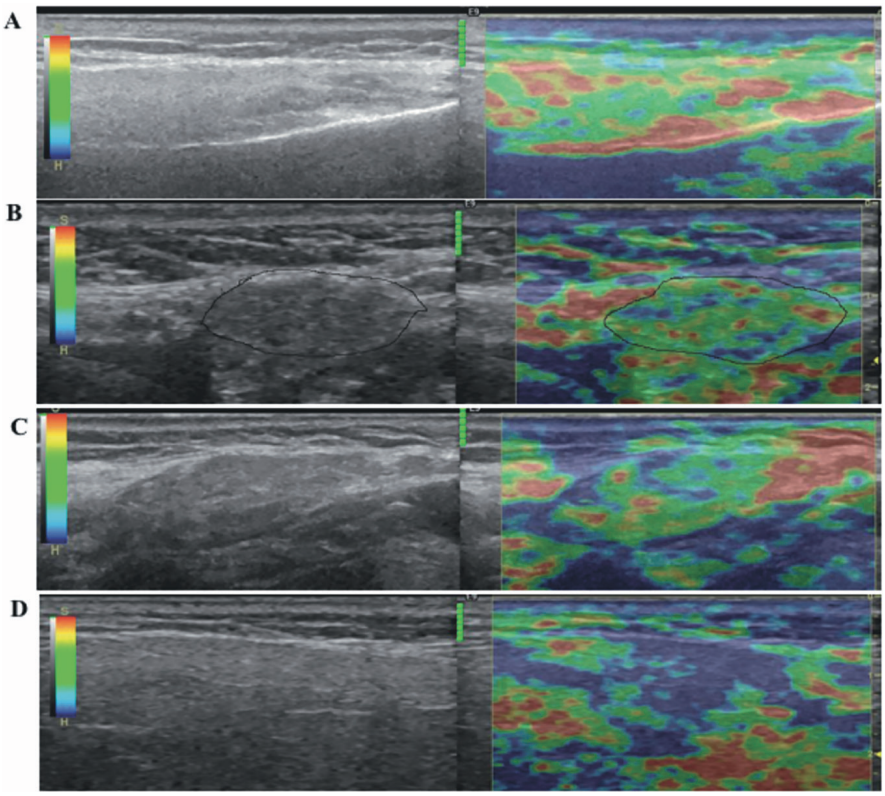


Fig. 1. Representative images showing the elasticity scores of major salivary glands.
A: Score 1: Partially mottled red regions (10-50%) are shown in the light green coloured area (parotid gland).
B: Score 2: The entire coloured area is shown as relatively uniform light green (submandibular gland). A region of interest (ROI) was selected including the lesions and the surrounding parenchyma.
C: Score 3: Light green and blue are mixed in the coloured area, mainly green (>50%) (submandibular gland).
D: Score 4: Light green and blue are mixed in the coloured area, mainly blue(>50%) (parotid gland).

Sonoelastography

SE examinations of the major salivary glands of all subjects were processed by the same examiner (S.Z.), who has 25 years' experience and was blinded to the clinical data. Sonoelastographic images were acquired in real time with a 12 MHz transducer (GE logic E9, Agile, America). Longitudinal and transverse imaging of the glands was performed using real-time B-mode US. Then, switching to the elastography mode, the transducer position was consistent with those of conventional US. Using the B mode display for guidance, a region of interest (ROI) was selected including the lesions and the surrounding parenchyma. The elastographic images and the corresponding B-mode image were simultaneously displayed on the monitor. This configuration made it possible to check positioning of the ROI during examination. Sonoelastographic images were obtained with appropriate compression manually along with the axis of US beam (22). During the examination, the computer indicated whether the manual compression was adequate on a colour scale ranging from 1 to 7. The compression was deemed valid when the value was ≥5. The softest component was described in red, indicating the greatest strain, whereas the hardest component with lowest strain was depicted in blue; green showed intermediate elasticity. Filing of the elastographic images took place in real time, and the images were adequate when the colour within the ROI was constant for ~5s. The

Table I. General characteristics of the study population.

Characteristics	pSS patients (n=79)	Non-pSS subjects(n=54)				
		Sicca syndrome (n=10)	Hypothyroidism (n=5)	SLE (n=6)	RA (n=18)	Healthy subjects (n=15)
Age, mean±SD, years	55.96±10.8	52.5±9.25	48±12.94	37.83±6.79	61.50±13.86	51.73±15.13
Female/male	75/4	9/1	4/1	6/0	15/3	15/0
[a]Symptom duration, years	6 (0.1, 27)*	3.5 (1,10)	2 (1, 4)	2 (0.1, 11)	9 (3, 30)	0
Xerostomia	73 (92.4)*	9 (90)	2 (40)	5 (83.3)	16 (88.9)	0
Xerophthalmia	68 (86.1)*	7 (70)	0	1 (16.7)	2 (11.1)	0
[b]Schirmer I tesr	55/58*	0	0	1/2	0/1	0
[b]Sialoscintigraphy	21/24*	0	0	0	0	0
[b]MSG biopsy	32/39*	0	0	0	0	0
[b]Anti-SSA	43/63	0/5	0	5/6	8/15	0
[b]Anti-SSB	23/64*	0/5	0	0/6	0/15	0

Except where indicated otherwise, values were the number (%).
[a]Non-normally distributed measurement data were given as median (minimum, maximum).
[b]Values of objective tests given as rates of positive results (positive/total).
p-values determined using Student *t*-test, Mann-Whitney test, or chi-square test, as appropriate.
*$p<0.001$: statistically significant (comparing between pSS patients and non-pSS subjects).
MSG: minor small labial gland.

process was repeated 3-5 times until a good-quality and stable elastographic image was obtained. Since there is no standardised method of interpreting elastograms qualitatively in the salivary glands, we classified the lesions on the basis of a 4-point scoring method adapted from the hepatic fibrosis with chronic hepatitis C score (Fig.1A-D) (23): score 1: Partially mottled red regions (10–50%) are shown in the light green coloured area; score 2: The entire coloured area is shown as relatively uniform light green; score 3: Light green and blue are mixed in the coloured area, mainly green (>50%); score 4: Light green and blue are mixed in the coloured area, mainly blue (>50%). In each patient, 4 points were obtained. Parotid and submandibular glands using B-mode ultrasonography were individually evaluated for parenchymal echogenicity, homogeneity, hypoechogenic areas, hyperechogenic reflections and clearness of borders (range 0–48) (24). The scores of bilateral parotid glands, accompanied with the scores of bilateral submandibular glands and the sum of all four glands were considered in the analysis.

Statistical analysis

All statistical analyses were performed using Statistical Package of Social Science (SPSS) software version 16.0. For statistical comparisons, the Student's *t*-test, Mann-Whitney test, or chi-square test were used, as appropriate. Spearman's test was used for correlation analysis. *p*-values less than 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves were used to describe the diagnostic performances of SE. The optimal cut-off point producing the maximal combination of sensitivity and specificity were determined, as well as negative and positive predictive values.

Results

Characteristics of the study subjects

As shown in Table I, detailed profiles of the study subjects were presented. Seventy-nine subjects fulfilled the criteria for inclusion in the pSS group (female/male ratio 75/4; age 55.96±10.8 years; symptom duration 0.1-27.0 years). The control group comprised a total of 54 subjects: 39 non-SS patients with idiopathic Sicca syndrome (n=10), hypothyroidism (n=5), rheumatoid arthritis (RA; n=18), systemic lupus erythematosus (SLE; n=6), and 15 healthy subjects (female/male ratio 49/5; age 53.2±14.4 years). No statistically significant differences were found between the groups in terms of age, sex ratio, or the presence of anti-SSA antibody (p=0.24, 0.344, 0.787, respectively). However, the frequency of xerostomia and xerophthalmia was significantly higher in the pSS group than the control group ($p<0.001$, both). Further, the pSS group also showed a significantly higher frequency of the presence of anti-SSB antibody and positive findings in Schirmer test, sialoscintigraphy, and positive MSG biopsy ($p<0.001$, overall), as compared to the control group.

Features of SE and US in pSS

When it comes to the elastographic qualitative scores of bilateral parotid, submandibular glands, and the sum of all four glands, no significant difference was found between disease controls and healthy subjects ($p>0.05$, overall). Then, we separately compared the elasticity scores in pSS group with disease controls and healthy subjects. The elasticity scores in the pSS group were significantly higher than those in the disease controls ($p<0.001$, overall). Similar trend was found between the pSS group and healthy subjects ($p<0.001$, overall). Further, the elasticity scores of bilateral parotid, submandibular glands, and the sum of all four glands in the pSS group were strikingly higher than those in the control group ($p<0.001$, overall) (Fig. 2). Our study also showed significant difference between parotid and submandibular scores ($p<0.001$). No statistically significant correlation was found between the age distribution and elasticity scores ($p>0.05$).

For B-mode ultrasonography, the scores of bilateral parotid, submandibular glands and the sum of all four glands in the pSS group were signifi-

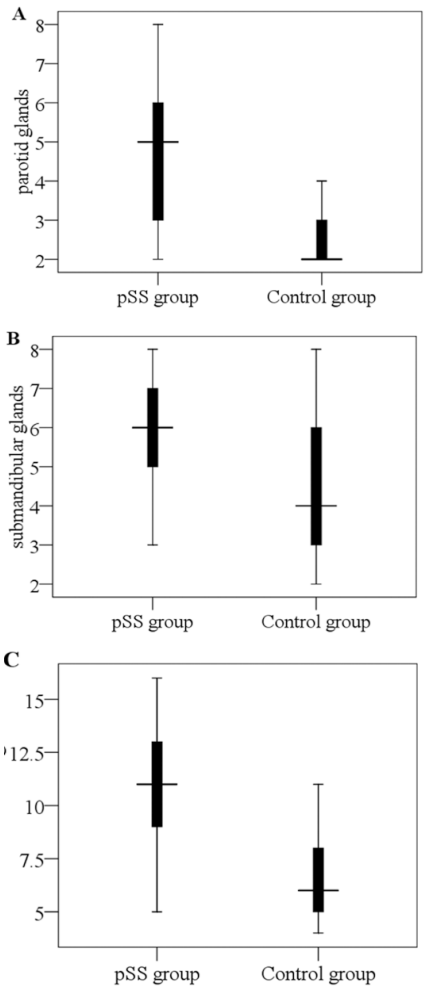
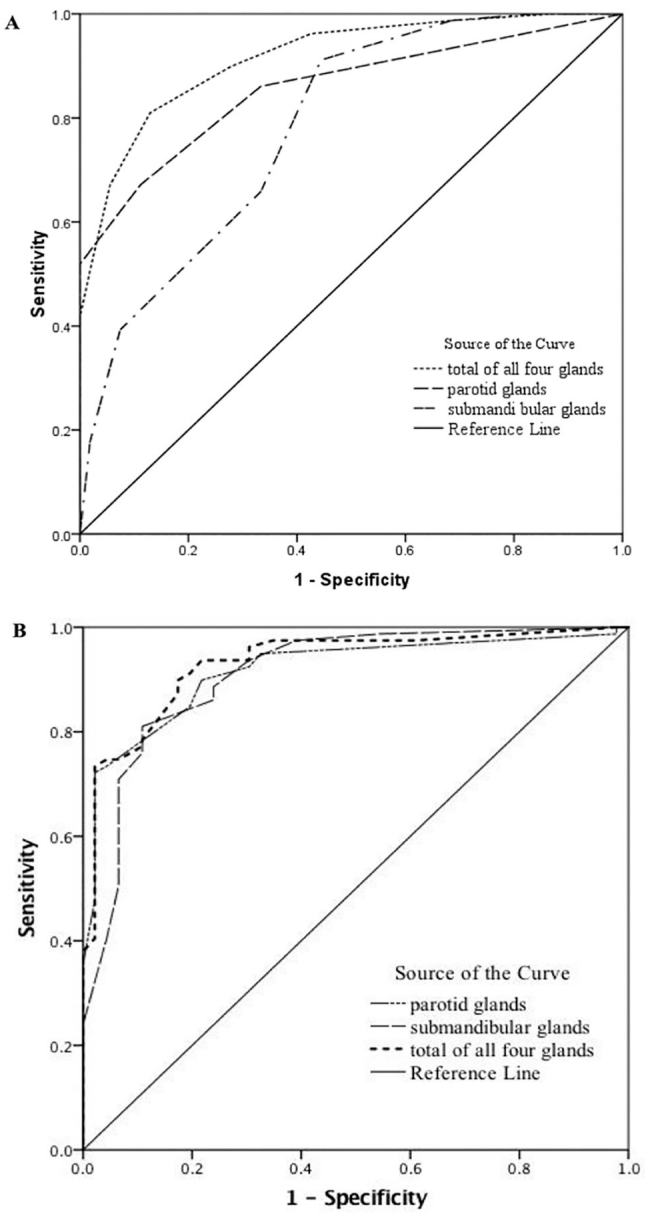


Fig. 2. Distribution of the sonoelastographic qualitative scores for the pSS group and control group.
A: Distribution of the scores of bilateral parotid glands.
B: Distribution of the scores of bilateral submandibular glands.
C: Distribution of the sum of scores of all four glands.

Fig. 3. ROC curves presented the diagnostic accuracy of the SE and US.
A: For the SE, the total AUC-ROC of all four glands was the maximum score (0.916).
B: For the US, the sum of all four glands produced the highest AUC-ROC (0.932).



cantly higher than those in the control group (p<0.001, overall).

Diagnostic value of SE and US in pSS

ROC curve analysis was used to explore and compare the preliminary diagnostic accuracy of SE using different calculated scoring methods (Fig. 3A). The sum of the scores of all four glands provided the largest AUC-ROC (0.916, 95% CI 0.87–0.962), compared with that of bilateral parotid glands (0.857, 95% CI 0.794–0.919) and that of bilateral submandibular glands (0.783, 95% CI 0.704–0.863). The optimal cut-off value of the total scores of all four glands for pSS was 9 and was associated with the best 81% sensitivity, 87% specificity, 90.1% PPV and 75.8% NPV (Table II).

For US, combined evaluation of both parotid and submandibular glands (AUC-ROC: 0.932, 95% CI 0.888-0.977) showed better diagnostic accuracy than bilateral parotid (AUC-ROC: 0.917, 95% CI 0.868-0.967) or submandibular glands (AUC-ROC: 0.910, 95% CI 0.856–0.965) evaluation (p<0.001, overall) (Fig. 3B). An optimal US cut-off value of 15 for total four glands provided maximal sensitivity (87.7%) and specificity (82.6%).

Correlation between SE and disease characteristics of pSS

We found higher scores of bilateral parotid glands in pSS patients complicated with dental loss symptom (p=0.006), but not for submandibular elasticity scores (p>0.05). Correlation analysis suggested a positive correlation between the scores of bilateral parotid glands and disease duration (Spearman r=0.244, p=0.03, respectively), but not for the bilateral submandibular gland scores (Spearman r=0.091, p=0.424, respectively). The scores of bilateral parotid glands witnessed significant differences between disease duration ≤5 years and >10 years (p=0.007) and between 5–10 years and >10 years (p=0.009), but not between the disease duration ≤5 years and 5–10 years (p=0.952) (Fig. 4). However,

Table II. Cut-off values for the diagnosis of pSS with qualitative scoring method.

	Area under the curve	Cut-off value	Sensitivity	Specificity	PPV	NPV
Parotid glands	0.857	4	67.1%	88.7%	89.8%	64.9%
Submandibular glands	0.783	5	91.1%	55.5%	75%	81.1%
Total of four glands	0.916	9	81%	87%	90.1%	75.8%

PPV: positive predictive value; NPV: negative predictive value.

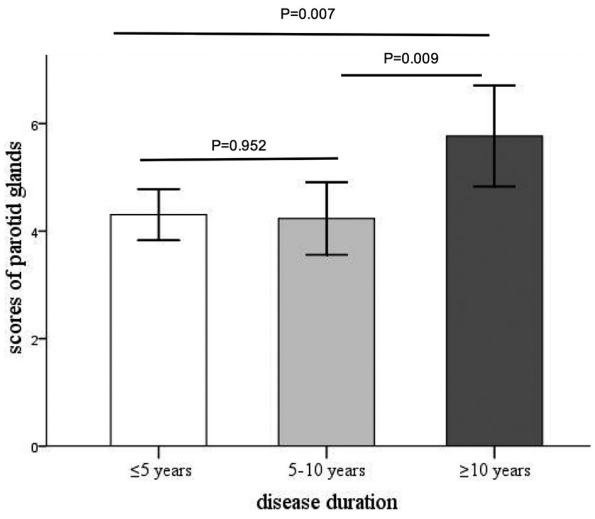


Fig. 4. Association between the elasticity scores of the parotid glands and disease duration.

there was no difference among three groups for the scores of bilateral submandibular glands (p>0.05).

Given that serological parameters played a pivotal role in the diagnosis of pSS, we associated sonoelastographic scores with serological parameters as well. Data showed that total of parotid and submandibular glands were correlated with the level of RF (spearman r=0.297, p=0.015). However, we did not find any correlation between SE scores and IgG, anti-SSA positivity, anti-SSB positivity and ESSDAI (EULAR SS disease activity index, ESSDAI) (p>0.05, overall).

Discussion

To date, a precise and feasible evaluation method for pSS remains to be established. SE emerged as a rapidly developing imaging technique, is available for predicting histology, in which tissue contrast is derived from relative differences in mechanical stiffness. The observation that infiltration of tissue of autoimmune exocrinopathy for pSS by mononuclear cells results in the replacement of epithelial structure by fibrous tissue along with the progress of the disease is acknowledged (25). It seems that the more serious the disease and the more fibrous texture replacement of salivary glands, the stiffer the salivary glands. On the basis of different elastic properties, we applied SE to assess salivary diffuse pathologic lesions for pSS.

The current study consisted of two parts: the diagnostic value and clinical evaluation of elasticity scoring for pSS. For the qualitative analysis, the sonoelastographic scores in pSS group tended to be considerably higher than those of non-pSS. These findings indicated that there were detectable differences in the stiffness of salivary lesions between pSS and non-pSS patients using qualitative elastographic scoring method. ROC curves evaluated the diagnostic value of sonoelastographic qualitative 4-point score for pSS. The AUC-ROC showed that combined evaluation of all four glands had the best diagnostic accuracy for pSS, compared with single evaluation of bilateral parotid or submandibular glands. The optimal cut-off value was 9 for combined evaluation of all four glands (81% sensitivity and 87% specificity, respectively). Christian *et al*. ever reported a cut-off of ≥6 for the real-time SE semi-quantitative score, which achieved a sensitivity of 66.7% and a specificity of 85.7% for the diagnosis of pSS (18). The alterations in different studies about the ratios may be attributed to different scoring systems and sets of control groups. To this end, a larger cohort of samples is warranted to validate the performance of SE with elasticity scoring in the future.

In terms of clinical evaluation, we found higher scores of bilateral parotid glands in pSS patients complicated with dental loss symptom (p=0.006), but not for submandibular elasticity scores (p>0.05), which showed the involvement of parotid glands. However, we did not find any correlation between SE scores and IgG, anti-SSA positivity and anti-SSB positivity and ESSDAI (p>0.05, overall). A body of correlation analysis indicated that elasticity of bilateral parotid glands was associated with the disease duration. For the elasticity of bilateral parotid glands, there existed significance difference between middle and advanced stage, not for the early stage. These results are accordant with our assumption indicating that SE provides limited value for the diagnosis of early stage of pSS. Similarly, Emetullah *et al*. also reported that significant correlation was found in the average strain ratios of parotid gland between disease duration ≤5 years and >10 years, but not for submandibular glands (13). Why the scores of submandibular glands are not related with disease duration is not easily explained. Larger prospective studies are needed to verify it.

To be mentioned, there also occurred other types of elastographic examinations. Virtual acoustic radiation force impulse imaging (ARFI) is newly presented elastography technique which provide quantitative values by implementation short term acoustic force instead of manual compression. The advantage of ARFI technique is that the strength of acoustic radiation does not require external compression, and acoustic radiation of short duration generates tissue displacement. Quantitative ARFI imaging includes two modes:

Virtual Touch tissue quantification (VTQ) and Virtual Touch tissue imaging quantification (VTIQ). Our previous study worked on a small group and showed that the stiffness of the major salivary glands using VTQ and VTIQ in patients with pSS was increased compared with that of healthy controls (14). Although some reports refer to the quantitative assessment (the strain ratios) of stiffness, the current researches proposed so far have not further documented a standardised and stationary tissue that can be used as a reference and it requires additional calculation and time according to the elasticity map (26). What is more, some studies suggested that the strain ratio calculation did not provide additional data to the stiffness scores for the differentiation of nodules (8), which remains the sonoelastographic benchmark.

Our study did have certain limitations. First, the size of study population was relatively small, although it included different stages of disease. Second, as a highly operator-dependent technique, SE is manual compression in our study and the evaluation of inter-observer variability was ignored when scoring. However, our operational process was repeated 3-5 times until a good-quality and stable elastographic image was obtained. It is believed that accuracy would be greatly improved after the evaluator has become accustomed to the procedure. In future, large-scale studies with analysing inter and intra-reader repeatability will better delineate the usefulness of SE in the diagnosis of pSS.

Conclusion

Major salivary gland elastography, performed simultaneously with B-mode ultrasound, holds promise as an adjunct in the diagnosis of pSS and can serve as a feasible tool in clinical practice. Further advances in ultrasonographic technology as well as large prospective studies will better delineate the usefulness of SE in the field of pSS.

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