Journal of Dental Sciences 19 (2024) 2179–2185

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Original Article

The value of parotid sialography in the diagnosis and staging of Sjogren's syndrome

Yutian Wang [a], Xiaoyan Xie [b], Ying Han [a], Xingyun Liu [a], Qianyun Guo [a], Lei Zhang [a], Xinyi Ni [a], Hongwei Liu [a*]

[a] *Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China*
[b] *Department of Oral and Maxillofacial Radiology, Peking University School and Hospital of Stomatology, Beijing, China*

Received 29 January 2024; Final revision received 6 March 2024
Available online 19 March 2024

KEYWORDS
Parotid sialography;
Sjogren's syndrome;
Staging;
Retrospective study;
Lymphoma

Abstract *Background/purpose:* 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) primary Sjögren's syndrome (SS) diagnostic criteria did not incorporate radiographic examination while staging SS according to salivary gland imaging and serological autoantibody tests was not discussed. The aim is to study the value of parotid sialography for diagnosing SS, and to initially explore the method of staging SS based on the results of imaging and serological autoantibody tests.
Materials and methods: 287 patients' clinical records were included. The sensitivity and specificity of parotid sialography in the diagnosis of SS were investigated. SS patients were categorized into early stage (autoantibody positive, imaging does not support SS), active stage (autoantibody positive, imaging supports SS), and quiescent stage (autoantibody negative, imaging supports SS), clinical characteristics of different stages were compared.
Results: The sensitivity of parotid sialography for the diagnosis of SS was 82.6%, the specificity was 71.5%. 10-minute USFR of the patients in the active stage (0.18 $\pm$ 0.38 ml/10min) was significantly lower than that of early stage (0.34 $\pm$ 0.47 ml/10min) and quiescent stage (0.54 $\pm$ 0.52 ml/10min), $P = 0.010$, and the rate of confirmed SS was significantly higher in the active stage (82.9%) than that in the early stage (44.4%) and the quiescent stages (14.8%), $P < 0.001$.
Conclusion: Parotid sialography remains valuable in the diagnosis of SS. Performing imaging and serological autoantibody tests before lip gland biopsy may reduce invasive examinations for patients without significantly increasing the rate of missed diagnosis. According to imaging

* Corresponding author. Department of Oral Medicine, Peking University School and Hospital of Stomatology, 22 Zhong Guan Cun South Street, Haidian District, Beijing, 100081, China.
E-mail address: hongweil2569@163.com (H. Liu).

https://doi.org/10.1016/j.jds.2024.03.007
1991-7902/© 2024 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

and serological autoantibody tests, SS can be categorized into early, active, and quiescent stages.
© 2024 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease involving exocrine glands.[1] The prevalence is 0.03%—0.1%.[2] The international diagnostic criteria for SS have undergone many changes, and the most up-to-date SS diagnostic criteria is the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) primary SS diagnostic criteria.[3] The criteria did not incorporate radiographic examination. There is a lack of standardized criteria for the diagnosis and treatment of clinically atypical patients who do not meet this diagnostic criterion (e.g, autoantibody-negative patients with signs of salivary gland damage, etc.), and there is some disagreement as to whether lip gland biopsy should be routinely performed in these patients.[4]

Parotid sialography is a classical imaging method as an adjunct to salivary gland diseases,[5,6] It can effectively differentiate obstructive parotitis, parotid tumors, and SS. The sensitivity of salivary gland imaging for the diagnosis of SS is around 60—85%, including parotid sialography (sensitivity 76.5%—80.0%), salivary gland ultrasound (sensitivity 59.4%—85.7%),[7,8] etc. Not all SS patients present with imaging manifestations of salivary gland destruction, so it may be assumed that salivary gland destruction is a phenomenon that occurs after SS has progressed to a certain stage. The currently available EULAR Sjogren's syndrome disease activity index (ESSDAI) does not address salivary gland function assessment.[9] The Sjögren's Tool for Assessing Response in Sjogren's syndrome (STAR) mentions assessment of SS efficacy by ultrasound imaging while staging according to salivary gland imaging was not discussed.[10]

Therefore, the purpose of this study was to investigate the value of parotid sialography for the diagnosis of SS and to preliminarily explore a new method for clinical staging of SS based on salivary gland imaging and serum autoantibody findings.

Materials and methods

Clinical information

In this study, we reviewed our clinical records of 287 patients who attended the Department of Oral Medicine of Peking University Stomatology Hospital and completed parotid sialography from November 2018 to November 2022 (Fig. 1). Their gender, age, the presence of dry mouth or dry eye symptoms, 10- minute unstimulated salivary flow rate (USFR), the results of dry eye examinations (including the Schmidt's test, tear film break-up test, fundus fluorescence, and whether dry eye was diagnosed or not), results of salivary fungal cultures, and results of serologic tests (181 cases in total), including SSA antibody, SSB antibody, and other autoantibodies such as immunoglobulin, rheumatoid factor, anti-streptococcal O hemolysin, etc. And 13 of these patients underwent lip gland biopsy. Missing data were handled by exclusion in relative analysis as well as by the worst-case imputation.

Parotid sialography methods

The routine sialography methods used in our department is described below. The patient takes a seated position, the buccal part is pulled outward with an orofacial mirror to expose the mouth of the parotid catheter, using a 5 ml flusher to probe into the catheter from the mouth of the catheter, and then slowly push the contrast agent (Ioversol injection, specification: 20 ml:13.56 g)2—2.5 ml. Immediately take pictures of filling-stage X-rays; with 10% citrate solution in mouth, after 5 min, take pictures of emptying-stage X-rays. The radiologist read the films and record the morphology of the dominant parotid duct, branch duct morphology, terminal duct morphology, and emptying stage contrast residue, etc. The above results will be combined to determine whether the patient's parotid sialography is consistent with SS or other salivary gland diseases.

Sjogren's syndrome diagnostic criteria

SS were diagnosed according to the ACR/EULAR criteria.[3]

Sjogren's syndrome staging

Oral staging of SS progression of SS is based on autoantibodies and salivary gland imaging findings:

(1) Early stage: Positive serum antibodies and negative salivary gland imaging. Autoimmune disorders exist, but salivary glands have not yet developed imaging-observable destruction.
(2) Active stage: Positive serum antibodies and positive salivary gland imaging. Autoimmune disorders has developed imaging-recognizable salivary gland destruction.
(3) Quiescent stage: Negative serum antibodies and positive salivary gland imaging. The autoimmune disorder is under control but imaging-observable salivary gland destruction has already been developed.

Statistical analysis

SPSS26.0 statistical analysis software (IBM, Armonk, NY, U.S.A) was used. The study calculated the sensitivity and

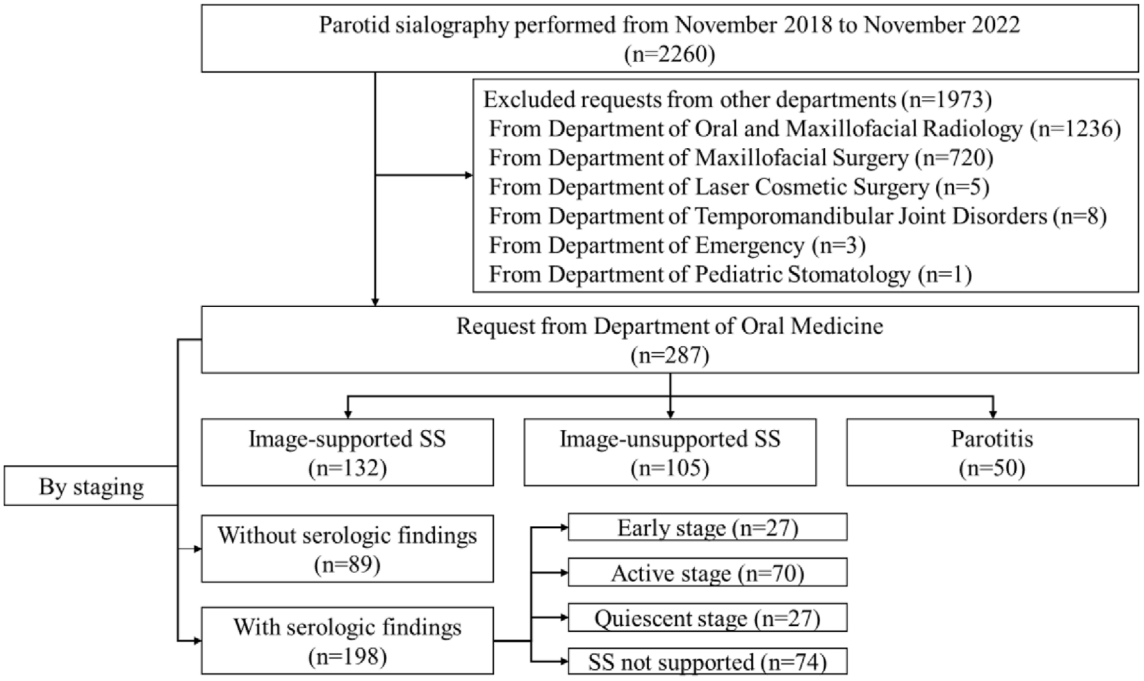

Figure 1 Flow of participants through study. Abbreviations: SS, Sjogren's syndrome.

specificity of parotid sialography. The diagnostic efficacy of parotid sialography for SS was assessed using receiver operating characteristic (ROC) curve and Area Under Curve (AUC). Comparisons between groups were made using the *t*-test for measurement data and the χ^2 test for count data, and comparisons between multiple groups were made using one-way ANOVA. Statistical significance was set at $P < 0.05$ unless otherwise indicated.

Results

Clinical information

This study included 132 cases of image-supported SS, 105 cases of image-unsupported SS (including normal images and other atypical results), and 50 cases of parotitis (including obstructive parotitis, chronic parotitis, etc.). The incidence of dry mouth in the contrast-diagnosed SS group (94.2%) was higher than in the image-unsupported SS group (87.6%), but the difference was not statistically significant. Lip gland biopsy was performed in 10 cases in the image-supported SS group and in 1 case in the image-unsupported SS group, and lymphocytic infiltration foci were detected in these patients. The 10-min USFR was lower in the SS group (0.25 ± 0.41vs 0.56 ± 0.79), and the positivity rate of serum autoantibodies (including SSA, SSB, etc.) was higher (72.9% vs 22.7%), higher rate of interference with feeding (57.1% vs 34.3%), higher rate of positive salivary fungal cultures (94.1%vs75.4%), and higher rate of confirmed diagnosis of SS according to the 2016 ACR/EULAR criteria ($P < 0.001$), as shown in Table 1. Three of the 50 patients in the mumps group were positive for autoantibodies, and another two patients were negative for autoantibodies but underwent lip gland biopsy with positive results; these five patients in the mumps group were diagnosed with SS. No adverse events were reported as a result of parotid sialography.

Diagnostic efficacy of parotid sialography

The sensitivity of parotid sialography for the diagnosis of SS was 82.6% (62/75), the specificity was 71.5% (88/123), the compliance rate with the gold standard was 75.8% (150/198), the positive predictive value was 63.9% (62/97), and the negative predictive value was 87.1% (88/101). See Table 2. The ROC curve was plotted, and its area under the curve was 0.755 (95% CI 0.686–0.825) (Fig. 2).

198 patients with serologic records were included in the combined trial study. Positive tandem test was defined as positive for both parotid sialography and serologic findings (any of the antibody positive, not only SSA or SSB), and the sensitivity of the tandem test was 82.9%, with a specificity of 90.2%, as shown in Table 3. Positive concurrent test was defined as positive for any one of the parotid sialography and serologic findings, and the sensitivity of the concurrent test for diagnosing SS was 98.7% and specificity was 59.3%. 98.7% of patients with negative parotid sialography and hematology were non-SS, shown in Table 3.

Clinical characteristics of patients with different stages of Sjogren's syndrome

According to the staging method described above, 198 patients with serologic findings were classified as early ($n = 27$), active ($n = 70$), and quiescent ($n = 27$); the

Table 1 Baseline characteristics of the study population.

Characteristics	Image-supported SS n = 132	Image-unsupported SS n = 105	$t/\chi 2$	P	Total n = 237
Age/years, $\bar{x} \pm s$	55.3 ± 14.1	57.2 ± 14.6	−1.012	0.312	56.91 ± 14.09
Female, n (%)	127 (95.5%)	95 (90.5%)	2.337	0.126	263 (93.7%)
Course of disease/months, $\bar{x} \pm s$	49.7 ± 73.2	26.8 ± 43.3	2.871	0.005	40.17 ± 63.03
Xerostomia, n (%)	125 (94.2%)	92 (87.6%)	5.136	0.077	217 (91.6%)
Dry eyes, n (%)	77 (57.9%)	53 (50.5%)	1.307	0.520	158 (54.9%)
Affects eating or swallowing, n (%)	76 (57.1%)	36 (34.3%)	18.086	< 0.001	127 (47.3%)
USFR/(ml/10min)	0.25 ± 0.41	0.56 ± 0.79	−2.983	0.004	0.33 ± 0.49
USFR < 0.1 ml/min, n (%)	66 (49.6%)	45 (42.9%)	3.434	0.180	111 (46.8%)
Diagnosed xerophthalmia, n (%)	37 (27.8%)	25 (23.8%)	0.775	0.679	73 (30.8%)
Salivary fungus culture positive, n (%)	96/102 (94.1%)	43/57 (75.4%)	18.127	< 0.001	139/159 (87.4%)
Serological test results exist, n (%)	96 (100.0%)	75 (100.0%)	/	/	171 (100.0%)
Positive indicators exist, n (%)	70 (72.9%)	17 (22.7%)	42.540	< 0.001	87 (50.8%)
Anti-SSA antibody positive, n (%)	49 (51.0%)	8 (10.7%)	30.887	< 0.001	57 (33.3%)
Anti-SSB antibody positive, n (%)	21 (21.9%)	4 (5.3%)	9.230	0.002	25 (14.6%)
Other antibody positive, n (%)	49 (51.0%)	15 (20.0%)	17.324	< 0.001	64 (37.4%)
2016ACR/EULAR criteria confirmed SS, n (%)	61 (63.5%)	9 (12.0%)	46.262	< 0.001	70 (40.9%)

Abbreviations: SS, Sjogren's syndrome; USFR, unstimulated salivary flow rate. The percentage denominator of the following items from the line with hematological examination results is the total number of serological examinations conducted in each group. Positive for other indicators refers to the positive result of any autoantibody indicator including antinuclear antibodies, immunoglobulins, anti-centromere antibodies, mitochondrial antibodies, rheumatoid factors, and anti-streptococcal O hemolysin, etc.

Table 2 Diagnostic efficacy of parotid sialography.

Parotid sialography/ gold standard	SS	SS not supported	Total
Positive	62	35	97
Negative	13	88	101
Total	75	123	198

Abbreviations: SS, Sjogren's syndrome.

other 74 patients did not support the diagnosis of SS on imaging and serum autoantibody tests.

10-min USFR of the patients in the active stage (0.18 ± 0.38ml/10min) was significantly lower than that of early (0.34 ± 0.47 ml/10min) and resting patients (0.54 ± 0.52 ml/10min), $P = 0.010$. Patients in the active stage had the highest rate of meeting the 2016 SS diagnostic criteria, followed by the early stage, and patients in the quiescent stage had the lowest rate. As shown in Table 4.

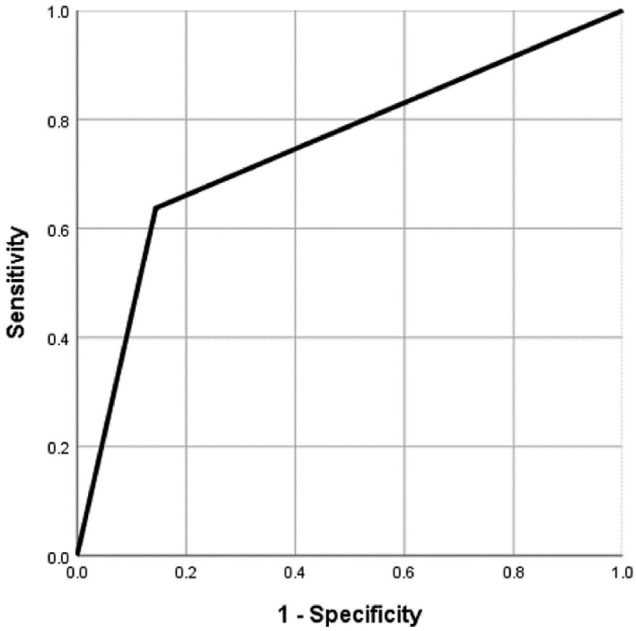

Figure 2 Receiver operating characteristic (ROC) curve of parotid sialography in diagnosis of Sjögren's syndrome. Area under the curve (AUC) was 0.755 (95% CI 0.686—0.825).

Discussion

Parotid sialography can effectively differentiate obstructive parotitis, parotid tumors, and SS, and is still used for imaging salivary gland diseases. In this study, we found that the sensitivity of parotid sialography for the diagnosis of SS was 81.6% and the specificity was 70.0%, which is similar to that reported in the previous literature.[7,8] Patients with negative parotid sialography and autoantibodies had a 98.5% probability of not being SS.

The iodine-containing contrast agents used for parotid sialography were previously thought to carry some risk of allergy, but Nadler retrospectively studied 1,515 patients undergoing parotid sialography and found no immediate or delayed allergic reactions,[14] the author accordingly concluded that suspicion of an allergy should not be regarded as a contraindication to salivary gland angiography.

Scholars have suggested that improved imaging may reduce the need for some unnecessary lip gland biopsies to

Table 3 Diagnostic efficacy of parotid sialography + autoantibody examination series test.

Parotid sialography	Serum autoantibody test	SS	SS not supported	Total
+	−	4	23	27
−	+	12	15	27
+	+	58	12	70
−	−	1	73	74
Total		75	123	198

Abbreviations: SS, Sjogren's syndrome.

be performed.[11] In the present study, fewer patients underwent lip gland biopsy, and the sensitivity and specificity of parotid imaging and autoantibodies were basically close to those of previous studies.[7] Therefore, it can be assumed that a portion of the cases included in this study were reduced in the performance of lip-gland biopsy procedures by improving the screening of parotid sialography, and this clinical strategy does not result in a significant increase in the rate of SS missed diagnosis. But still lack of lip gland biopsy results is one of the limitations of this study.

The likelihood of SS patients found to be negative for autoantibodies and parotid sialography in the present study was only 1.5%. This is similar to the results of the study by Mossel using salivary gland ultrasound, where the diagnosis of SS was fulfilled by only 2.2% (1/45) of the patients who were negative for both SSA and salivary gland ultrasound.[4] Patients who have met or excluded the diagnosis of SS by blood autoantibodies and imaging may not require additional lip gland biopsy.

Due to the increased risk of hematologic malignancies in SS patients (Standardized Incidence Ratio, SIR 11.55, 95% CI 4.32–30.90).[12] It has been found that germinal center-like lesions observed in lip gland biopsies, as well as salivary gland focus score can be used as predictive biomarkers for the early diagnosis of SS-associated lymphoma.[13,14] One patient with parotid gland swelling in this study died of pulmonary lymphoma one year after the diagnosis of SS. Lip gland biopsy may should be recommended in areas with a high incidence of lymphoma for early screening of lymphoma along with pathologic diagnosis of SS.

In this study, we proposed a staging method for SS based on imaging and serological autoantibody tests, and categorized SS patients into early, active, and quiescent stages. There was no significant difference in disease duration among the three groups, which may be due to the fact that the rate of disease progression of SS varies among individuals. In future studies, we intend to follow up a group of Early-stage patients and observe their disease progression and prognosis. The characteristics and therapeutic strategies of patients with different stages of SS may be different, which discussed in Table 5 referred to the existing SS guidelines.[15]

Oral fungal infection is the most frequent oral complication in SS. In this study, 91.1% (51/56) of the patients with confirmed SS were positive for salivary fungi, with strains of *Candida albicans* or *Candida klebsiella*. The main clinical symptoms of oral fungal infections are dry mouth, burning sensation, and painful eating irritation, which can exacerbate oral discomfort in patients with SS. Chen suggested that fungal infections are one of the early manifestations of Sjogren's syndrome.[16] *C. albicans* may associated with dental caries.[17]

SS patients can develop severe multiple caries due to reduced salivary buffering capacity and changes in the bacterial flora, which can manifest as multiple smooth surface caries, root surface caries. Severe dental caries can lead to the loss of teeth, which severely impacts the oral intake capacity of SS patients. Although recent studies have shown that topical fluoride and pilocarpine do not reduce the risk of caries in SS patients,[18,19] the 2016 EULAR recommendations on the treatment of SS with topical and systemic therapies and the 2017 British Rheumatism Association recommendations for the management of primary SS in adults recommend the use of regular oral examinations and the use of fluoride to prevent caries in patients with SS.[15,20]

Table 4 Clinical characteristics of SS patients at different stages.

Stages	Early stage n = 27	Active stage n = 70	Quiescent stage n = 27	$\chi 2/F$	P	Total n = 124
Age/years, $\bar{x} \pm s$	63.4 ± 10.8	53.7 ± 14.0	58.6 ± 16.0	4.968	0.008	56.9 ± 14.3
Female, n (%)	22 (81.5%)	68 (97.1%)	25 (92.6%)	7.101	0.029	115 (92.7%)
Course of disease/months, $\bar{x} \pm s$	48.8 ± 67.3	47.8 ± 72.2	49.1 ± 67.2	0.004	0.996	48.3 ± 69.6
Xerostomia, n (%)	23 (85.2%)	68 (97.1%)	25 (92.6%)	4.668	0.097	116 (93.5%)
Dry eyes, n (%)	14 (51.9%)	41 (58.6%)	16 (59.3%)	0.416	0.812	71 (57.3%)
Affects eating or swallowing	12 (44.4%)	41 (58.6%)	15 (55.6%)	1.577	0.454	68 (54.8%)
10minUSFR/(ml/10min)	0.34 ± 0.47	0.18 ± 0.38	0.54 ± 0.52	4.838	0.010	0.30 ± 0.45
USFR < 0.1 ml/min, n (%)	19 (70.4%)	55 (78.6%)	12 (44.4%)	10.694	0.005	86 (69.4%)
Diagnosed xerophthalmia, n (%)	5 (21.7%)	22 (32.8%)	7 (28.0%)	1.546	0.819	34 (29.6%)
Salivary fungus positive, n (%)	15/17 (88.2%)	53/57 (93.0%)	44/49 (89.8%)	0.521	0.771	112/123 (91.1%)
2016ACR/EULAR criteria confirmed SS, n (%)	12 (44.4%)	58 (82.9%)	4 (14.8%)	40.816	< 0.001	74 (59.7%)

Abbreviations: SS, Sjogren's syndrome; USFR, unstimulated salivary flow rate; ACR/EULAR, American College of Rheumatology/European League Against Rheumatism.

Table 5 Discussion on clinical characteristics and treatment strategies of SS patients with different stages.

Stage	Parotid sialography	Blood autoantibody test	Description	Treatment strategies
Early stage	−	+	In the early stage of the disease, there are active autoantibodies, but there is no visible destruction of the salivary glands on imaging	By immunomodulatory therapy, the level of autoantibodies can be reduced and salivary gland damage may be reduced; prevent possible fungal infections, dental caries, etc.
Active stage	+	+	During the active stage of the disease, there are active autoantibodies and visible destruction of the salivary glands has been formed through imaging	Immunomodulatory therapy to reduce autoantibody levels; simultaneously diagnose and treat existing oral fungal infections, implement three-level prevention strategies for dental caries, etc.
Quiescent stage	+	−	During the quiescent stage of the disease, there are no active autoantibodies, but imaging visible destruction of the salivary glands has been formed	The primary focus is to diagnose and treat oral complications, particularly fungal infections and dental caries. Monitoring autoantibody levels to prevent the recurrence of immune disorders.
SS not supported	−	−	Basically excluding SS	Diagnose and treat possible diseases such as parotitis, using local symptomatic measures (such as dilation and flushing, massage of the gland, etc.); look for other possible causes of dry mouth, such as medication use, mouth breathing, fungal infections, etc.

Abbreviations: SS, Sjogren's syndrome.

There are limitations in this study. Fewer performed lip gland biopsies may increase the risk of missed diagnoses, although this bias may be small. In addition, the relationship between mumps and SS was not discussed in this study. In the future, we plan to conduct prospective studies to examine the prognosis of patients with SS in different stages.

Parotid sialography radiography is valuable in the diagnosis of SS. Performing imaging and serological examinations before performing lip gland biopsy may reduce the performance of some biopsy procedures without causing a significant increase in the rate of missed diagnosis. The disease process in SS patients can be categorized into early, active, and quiescent stages according to imaging and hematology tests.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

None.

References

1. Mariette X, Criswell LA. Primary Sjögren's syndrome. *N Engl J Med* 2018;378:931—9.
2. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:1983—9.
3. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017;76:9—16.
4. Mossel E, Delli K, van Nimwegen JF, et al. Ultrasonography of major salivary glands compared with parotid and labial gland biopsy and classification criteria in patients with clinically suspected primary Sjögren's syndrome. *Ann Rheum Dis* 2017;76:1883—9.

5. Rose SS. Sialography in diagnosis. *Postgrad Med* 1950;26: 521—31.
6. Foggia MJ, Peterson J, Maley J, et al. Sialographic analysis of parotid ductal abnormalities associated with Sjogren's syndrome. *Oral Dis* 2020;26:912—9.
7. Song GG, Lee YH. Diagnostic accuracies of sialography and salivary ultrasonography in Sjögren's syndrome patients: a meta-analysis. *Clin Exp Rheumatol* 2014;32:516—22.
8. Takagi Y, Kimura Y, Nakamura H, et al. Salivary gland ultrasonography: can it be an alternative to sialography as an imaging modality for Sjogren's syndrome? *Ann Rheum Dis* 2010;69: 1321—4.
9. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome published correction appears in Ann Rheum Dis. *Ann Rheum Dis* 2011;70(5):880. 2010;69:1103-1109.
10. Seror R, Baron G, Camus M, et al. Development and preliminary validation of the Sjögren's Tool for Assessing Response (STAR): a consensual composite score for assessing treatment effect in primary Sjögren's syndrome. *Ann Rheum Dis* 2022;81:979—89.
11. Al Tabaa O, Gouze H, Hamroun S, et al. Normal salivary gland ultrasonography could rule out the diagnosis of Sjögren's syndrome in anti-SSA-negative patients with sicca syndrome. *RMD Open* 2021;7:e001503.
12. Zhong H, Liu S, Wang Y, et al. Primary Sjögren's syndrome is associated with increased risk of malignancies besides lymphoma: a systematic review and meta-analysis. *Autoimmun Rev* 2022;21:103084.
13. Chatzis L, Goules AV, Pezoulas V, et al. A biomarker for lymphoma development in Sjogren's syndrome: salivary gland focus score. *J Autoimmun* 2021;121:102648.
14. Theander E, Vasaitis L, Baecklund E, et al. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. *Ann Rheum Dis* 2011;70:1363—8.
15. Price EJ, Rauz S, Tappuni AR, et al. The British Society for Rheumatology guideline for the management of adults with primary Sjögren's Syndrome. *Rheumatology* 2017;56:1643—7.
16. Chen CL, Chang FC, Hung YM, et al. *Candida* infection as an early sign of subsequent Sjögren's syndrome: a population-based matched cohort study. *Front Med* 2022;8:796324.
17. Cvanova M, Ruzicka F, Kukletova M, et al. *Candida* species and selected behavioral factors co-associated with severe early childhood caries: case-control study. *Front Cell Infect Microbiol* 2022;12:943480.
18. Xin W, Leung KC, Lo EC, et al. A randomized, double-blind, placebo-controlled clinical trial of fluoride varnish in preventing dental caries of Sjögren's syndrome patients. *BMC Oral Health* 2016;16:102.
19. Hsu CY, Hung KC, Lin MS, et al. The effect of pilocarpine on dental caries in patients with primary Sjögren's syndrome: a database prospective cohort study. *Arthritis Res Ther* 2019;21: 251.
20. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020;79: 3—18.