At the cutting-edge

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EDITORIAL

At the cutting-edge: what's the latest in imaging to diagnose Sjögren's disease?

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Sjögren's disease (SjD) or Sjögren's syndrome is an autoimmune disease characterized by hypofunction of the salivary and lacrimal glands. Until now, we do not possess a gold standard to diagnose the disease, i.e. a single test with high sensitivity and high specificity which can successfully discriminate patients with SjD from non-SjD controls. As a result, different diagnostic tests are now implemented in the diagnostic workup and throughout the decades numerous classification criteria for SjD have been proposed. The 2016 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria are the most recent and popular ones [1]. Although salivary gland imaging has been extensively studied in SjD and the debate on including these tools is ongoing, it is not yet included as an item among these diagnostic and classification criteria. However, despite the fact that SjD is a clinical diagnosis, clinical symptoms are not always evident, and there is a place for imaging tools for both the diagnostic work-up as for monitoring disease activity/progression and response to treatment.

Previously, the imaging tools used to diagnose SjD were mainly sialography and salivary gland scintigraphy, which were also part of the older criteria. These tools which were predominantly intended in fact to classify whether a patient is eligible to be included in a study and to create homogenous patient populations of SjD patients for research purposes. Sialography is a technique in which a contrast medium is introduced in the ductal system of the gland leading to visualization of the ductal system. Characteristic, but not specific, for SjD is an extravasation of the contrast medium resulting in an image characterized as Apfelblüten or snowflakes. Similar features can also be seen in sialadenitis from other causes, e.g. in IgG-related sialadenitis. Furthermore, sialo-cone-beam computed tomography and magnetic resonance imaging (MRI) and MRI sialography, which have an increased spatial resolution, can both provide 3D images of the ductal system. MRI (sialography) has an added value in the diagnostic work-up and could be considered in patients suspected for SjD whose diagnosis remains unclear after ultrasound examination [2]. However, MRI sialography is not routinely applied in the diagnostic work-up of SjD. Salivary gland scintigraphy is a technique in which technetium-99 m (^{99m}Tc) pertechnetate is administered intravenously to the patient. ^{99m}Tc-pertechnate is taken up by the salivary gland epithelial cells [3]. In SjD there is as a delayed uptake, reduced concentration, and/or delayed excretion of this tracer. The specificity of salivary scintigraphy is moderate, and it is not possible to differentiate an uptake failure from a secretory failure [4]. Both techniques are not included in the 2016 ACR/EULAR classification criteria for SjD [1]. Furthermore, their diagnostic ability is now surpassed by newer techniques such as salivary gland ultrasonography (SGUS) and positron emission tomography (PET) [5,6]. Finally, sialoendoscopy is a tool in development for SjD, not so much for diagnostics, but for treatment [7].

With SGUS, usually both parotid and submandibular glands are scanned. A characteristic image is in homogeneity of the parenchyma with anechoic/hypoechoic areas (Figure 1) [8]. While SGUS is not yet part of the classification criteria, there are thoughts to add it to the classification criteria sets [9]. Studies have shown that by adding SGUS, the sensitivity and specificity of the criteria is particularly high and at the same time clinicians are offered a wider array of tests to evaluate patients with SjD. However, it has been shown that SGUS cannot replace neither a salivary gland biopsy nor sialometry, which are part of the classification criteria, because these tests measure different (or at best partly related) constructs [10]. As far as the accuracy of SGUS is considered in comparison to salivary gland biopsy, the specificity and sensitivity of SGUS do not yet allow for replacement of the biopsy in the diagnostic work-up of patients suspected for SjD [10]. Nevertheless, when SGUS is added to the classification criteria, the clinician has availability of a simple, easy to apply diagnostic test for assessing the involvement of the salivary glands in the disease. Combining SGUS with shear wave elastography of the major or minor salivary glands might even increase its diagnostic ability, and additionally it can better discriminate/assess the disease activity/progression of SjD [11]. Interestingly, combining SGUS with anti-SSA/Ro antibodies can be highly predictive of the classification of a patient [12]. SGUS is a quick screening

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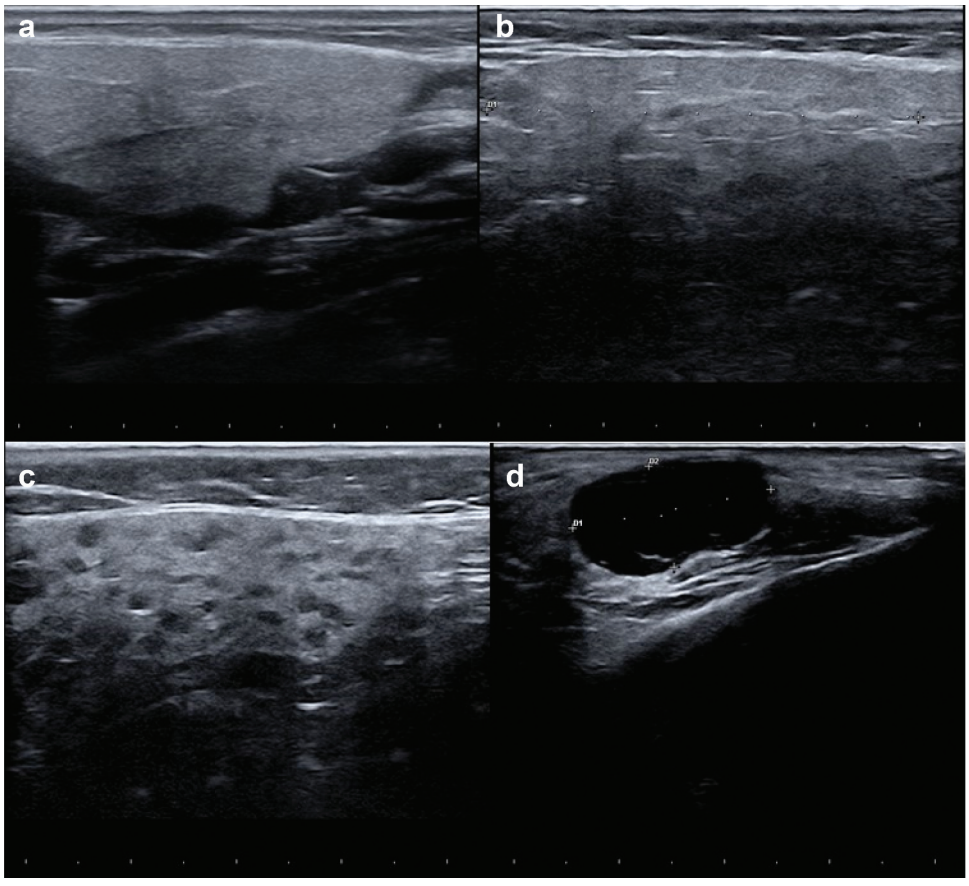

Figure 1. Representative SGUS images in SjD.

a. Parotid gland with normal echostructure. b. Parotid gland with mild inhomogeneity and a few hypoechoic areas. c. Parotid gland with severe inhomogeneity and multiple hypoechoic areas. d. Parotid gland with a histologically proven MALT lymphoma showing a nearly anechoic space-occupying lesion.

tool, but whether SGUS is useful for assessing disease activity and/or progression is under investigation and/or has yet to be proven. Recently, Sluijpers and colleagues showed in a well-described cohort of 253 patients with SjD that SGUS remained stable on a group level during a follow-up period of 5 years [13].

Numerous studies have been published showing the added value of SGUS in the 2016 ACR-EULAR classification criteria. However, none of these studies included a control group of patients with a disease mimicking SjD, like systemic sclerosis (SSc), hepatitis C, HIV, sarcoidosis, and IgG4-related sialadenitis [9]. For example, Hafez et al. [14] showed that approximately 66% of SSc patients exhibited glandular pathology. SSc patients showed a total parotid grayscale of 2, a total submandibular grayscale of 2, and a total glandular grayscale of 4 according to the OMERACT scoring system comparable to what can be seen in SjD.

An additional use of SGUS is as an aid for detecting lymphoma, in particular MALT lymphomas of the parotid gland. Lymphomas arise in 5–10% of the patients with SjD during the course of their disease and these lymphomas are often located in the parotid glands. With SGUS, the salivary glands parenchyma can be meticulously imaged and a core needle biopsy, guided by SGUS, can be easily taken to confirm that a lymphoma is present. The SGUS pattern in salivary gland MALT-lymphomas differs from a diffuse appearance with multiple hypoechogenic areas, to a more focal appearance with hypo-echogenicity, an oval shape, well-defined margins and internal hyperechoic septa (Figure 1) [15]. SGUS guided core needle biopsies are a promising technique and an alternative to salivary gland biopsies (labial, parotid) in case of a suspect for a MALT-lymphoma, since they require no anesthesia, adequate quality of the tissue can be sampled, and they are safe and highly acceptable by patients. However, during the diagnostic work-up of a patient, in particular when there are yet no signs of a MALT-lymphoma, a (parotid) salivary gland biopsy is preferred. There are also studies showing that SGUS can also be applied for the lacrimal gland as part of the diagnostic work-up as well as for detecting MALT lymphomas [16].

An emerging imaging technique in SjD-lymphoma diagnostics is PET, a nuclear imaging method in which a positron emitting radiopharmaceutical is injected intravenously. The most common tracer used in PET imaging is ^{18}F-fluorodeoxyglucose (FDG). PET is usually combined in a hybrid setting with computed tomography (CT). In SjD patients, FDG-PET/CT might have some diagnostic possibilities, but it is a great tool in assessing disease activity and progression, as well as staging a MALT lymphoma (Figure 2). Furthermore, it was found to be a highly sensitive and reliable tool to detect systemic manifestations in relation to a lymphoma including those in the salivary glands [6]. In the near future, also other, probably more specific, PET-tracers

will become available, for example for specific targeting of immune cell populations (lymphocytes, macrophages, and fibroblasts).

Up to now, MRI has been routinely used for the evaluation of pSS-associated lymphomas in the head and neck region (Figure 2). The solid cystic appearances of MALT lymphomas on an MRI can help to differentiate MALT from non-MALT lymphomas. MRI is used for local staging of the disease, by assessing the ingrowth in adjacent structures and spread to lymph nodes or other organs. Currently, MRI is, due to its high spatial resolution, the most useful imaging technique for local staging of pSS-associated salivary and lacrimal gland lymphomas.

With sialoendoscopy, the ductal system is directly visualized, so present constrictions can be directly widened, mucus plugs can be removed, and the ductal system is rinsed. Sialoendoscopy has no diagnostic use, but it might be of use in treating local activity in the salivary glands in patients with SjD. Previously, the experience with sialography has shown that the glandular symptoms can be reduced due to the introduction of the contrast medium into the ductal system. This is probably due to the rinsing of the ductal system, removing mucin plugs and other obstructions. The latter is probably responsible for most of the beneficial effects. It has been shown that sialendoscopy improves the glandular function by up to 12 months [7]. A newer method is contrast enhanced ultrasound sialendoscopy (CEUSS) in which the ductal system is rinsed with sulfur hexafluoride microbubbles [17]. In this way, the ductal system can be more easily opened and better rinsed. After CEUSS, both the unstimulated and stimulated whole saliva flow rate increased as well as the patient reported xerostomia complaints improved, at least in the short term. Further study is needed to prove that CEUSS indeed improves salivary gland functioning in SjD.

Summarizing, studies so far show that imaging techniques have a high potential not only for diagnosing and classifying SjD, but also for monitoring disease activity and disease progression, and potentially local treatment (Table 1). Furthermore, they make differentiation between SjD, and MALT lymphomas possible and are, e.g. FDG-PET/CT, able to visualize systemic manifestations of both SjD and lymphomas. While the role of sialography and salivary gland scintigraphy in diagnosing SjD has been reduced, newer techniques such as SGUS, MRI, FDG-PET/CT and to a certain extent sialendoscopy have taken over. Although these imaging techniques, in contrast to tear gland evaluation, are not yet part of the classification criteria, they have great potential to facilitate different aspects in which the

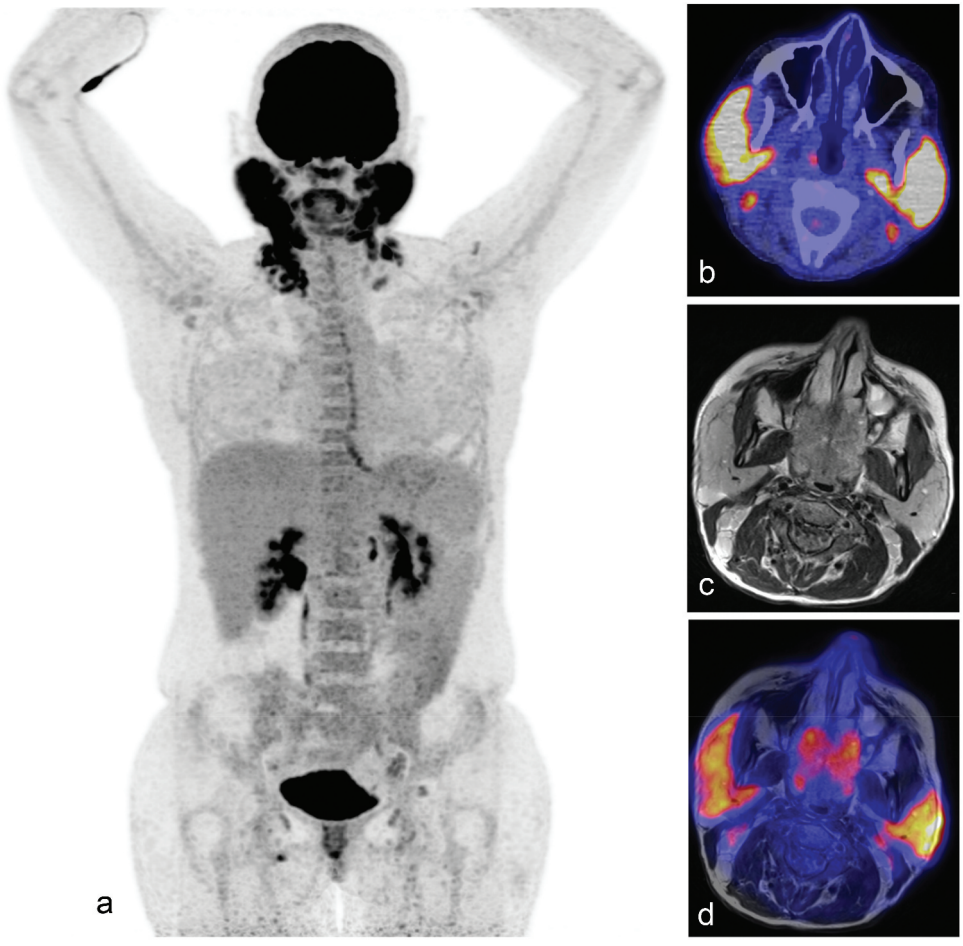

Figure 2. 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) findings in a SjD patient with salivary gland mucosa associated lymphoid tissue (MALT) lymphoma.

a. Whole-body FDG-PET showing intense FDG-uptake in both parotid glands, the submandibular glands and lymph nodes in the head/neck and supraclavicular regions. Increased FDG-uptake (to a lesser extent) was also found in lymph nodes in the axillary and inguinal regions. b. Fused FDG-PET/CT image showing enlarged parotid glands with intense FDG-uptake and lymph nodes with increased FDG-uptake. c. T2 MRI image showing diffuse enlargement of the parotid glands, with homogeneous hyperintense signal. d. Fused transversal FDG-PET/MRI image showing heterogeneous FDG-uptake in both parotid glands and physiological uptake in the adenoids.

Table 1. Contribution of imaging techniques to the diagnostic work-up, progression, disease activity, and treatment of pSS patients (modified after van Ginkel MS, Glaudemans AWKM, van der Vegt B, et al., imaging in primary Sjögren's syndrome. J Clin Med. 2020;9(8)4292).

	Contribution to:				Involved in treatment of SjD:			
	Diagnosing pSS	Assessing SjD disease activity/ disease progression	Diagnosing SjD associated lymphoma	Staging SjD associated lymphoma	Treatment effect	Assessment of treatment response	Advantages	Disadvantages
Salivary glandbiopsy	+++	+	+++	-	-	++	– Gold standard of salivary and lacrimal gland MALT lymphoma diagnosis	– Invasive – Risk of sampling error
Sialography	+	+	-	-	?	-	– Moderate to high sensitivity and specificity	– Invasive – Contrast medium
MRI	+	+	+	+	-	?	– High spatial resolution – Useful in local staging of Sjögren associated lymphomas in the salivary and lacrimal glands	– Expensive – Moderate differentiation between benign and malignant lesions of the salivary and lacrimal glands
Ultrasound	++	+	+	+	?	+	– Diagnostic scoring system (OMRACT) – Non-invasive – WFast and easy to perfom – Non irradiating – Great aid for taking core biopsies	– Using OMRACT needs experience – Not all outpatient clinics have an ultrasound devise available
Sialoendoscopy	-	-	-	-	++	+	– Possible therapeutic effect of rinsing the ductal system – CEUSS may provide an extra effect	– Invasive – No added value in diagnostic work-up
Scintigraphy with ^{99m}Tc-pertechnetate	+	+	-	-	-	+	– Possibility of whole-body imaging	– Low specificity – Low spatial resolution
^{18}F-FDG-PET/CT	+	++	+	+++	-	+	– Whole-body imaging – Useful in assessing treatment response – Objective quantification possible	– Expensive – No exact interpretation criteria for SjD available

MRI: magnetic resonance imaging; PET/CT: positron emission tomography/computed tomography; MALT: mucosa-associated lymphoid tissue. Plus and minus signs are entered as follows: (+++) in case the imaging technique has an excellent contribution to the specific item, (++) for a good contribution, (+) in case the contribution is not yet clear or there is contradictory data, (-) in case there is no evidence for contribution of the imaging technique to the specific item, and (?) in case it is not yet known.

salivary glands are involved in patients with SjD, i.e. diagnosis, disease activity, monitoring, and treatment.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Shiboski CH, Shiboski SC, Seror R, et al. 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. 2016;76(1):9–16. doi: 10.1136/annrheumdis-2016-210571
2. Rao Y, Xu N, Zhang Y, et al. Value of magnetic resonance imaging and sialography of the parotid gland for diagnosis of primary Sjögren syndrome. Int J Rheum Dis. 2023;26(3):454–463. doi: 10.1111/1756-185X.14528
3. García-González M, González-Soto MJ, Gómez Rodríguez-Bethencourt MÁ, et al. The validity of salivary gland scintigraphy in Sjögren's syndrome diagnosis: comparison of visual and excretion fraction analyses. Clin Rheumatol. 2021;40(5):1923–1931. doi: 10.1007/s10067-020-05462-0
4. Huang J, Wu J, Zhao L, et al. Quantitative evaluation of salivary gland scintigraphy in Sjögren's syndrome: comparison of diagnostic efficacy and relationship with pathological features of the salivary glands. Ann Nucl Med. 2020;34(4):289–298. doi: 10.1007/s12149-020-01448-9

5. Hočevar A, Bruyn GA, Terslev L, et al. Development of a new ultrasound scoring system to evaluate glandular inflammation in Sjögren's syndrome: an OMERACT reliability exercise. Rheumatology (Oxford). 2022;61(8):3341–3350. doi: 10.1093/rheumatology/keab876
6. van Ginkel MS, Arends S, van der Vegt B, et al. FDG-PET/CT discriminates between patients with and without lymphomas in primary Sjögren's syndrome. Rheumatology (Oxford). 2023;9 (10):3323–3331. doi:10.1093/rheumatology/kead071
• **Describes FDG-PET/CT as a new potential tool for discriminating pSS patients with and without lymphoma**
7. Karagozoglu KH, Vissink A, Forouzanfar T, et al. Sialendoscopy increases saliva secretion and reduces xerostomia up to 60 weeks in Sjögren's syndrome patients: a randomized controlled study. Rheumatology (Oxford). 2021;60(3):1353–1363. doi: 10.1093/rheumatology/keaa284
8. Jousse-Joulin S, D'Agostino MA, Nicolas C, et al. Video clip assessment of a salivary gland ultrasound scoring system in Sjögren's syndrome using consensual definitions: an OMERACT ultrasound working group reliability exercise. Ann Rheum Dis. 2019;78 (7):967–973. doi: 10.1136/annrheumdis-2019-215024
• **A study showing the potential of the OMERACT scoring system for SGUS. Agreement was obtained to score only greyscale lesions and to focus on anechoic/hypoechoic foci in a semiquantitative matter or, if not possible on a qualitatively (present/absent) evaluation of fatty or fibrous lesions.**
9. van Nimwegen JF, Mossel E, Delli K, et al. Incorporation of Salivary Gland Ultrasonography into the American College of Rheumatology/European League Against Rheumatism Criteria for Primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2020;72 (4):583–590.
10. Mossel E, van Ginkel MS, Haacke EA, et al. Histopathology, salivary flow and ultrasonography of the parotid gland: three complementary measurements in primary Sjögren's syndrome. Rheumatology (Oxford). 2022;61(6):2472–2482. doi: 10.1093/rheumatology/keab781
•• **This study showed that histopathology, salivary flow and ultrasonography are complementary measurements and cannot directly replace each other in the workup of pSS.**
11. Özer H, Tezcan D, Hakbilen S, et al. Diagnostic performance of gray-scale ultrasound and shear wave elastography in assessing salivary gland involvement in patients with primary Sjögren's syndrome. J Clin Ultrasound. 2023;51(1):187–194. doi: 10.1002/jcu.23379
12. 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(1):e001503. doi: 10.1136/rmdopen-2020-001503
13. Sluijpers N, Delli K, de Wollf L, et al. Longitudinal evaluation of major salivary glands in primary Sjögren's Syndrome patients: data from the RESULT cohort. Clin Exp Rheumatol. 2023. accepted for publication
14. Hafez AE, Taha AM, Moshrif A, et al. Ultrasound abnormalities of the major salivary glands in Egyptian patients with systemic sclerosis. Clin Rheumatol. 2023 Sep 18;42(12):3351–3360. doi: 10.1007/s10067-023-06763-w
15. Zabotti A, Pegolo E, Giovannini I, et al. Usefulness of ultrasound guided core needle biopsy of the parotid gland for the diagnosis of primary Sjögren's syndrome. Clin Exp Rheumatol. 2022;40(12):2381–2386. doi: 10.55563/clinexprheumatol/5n49yj
16. Yang T, Delli K, Coumou AD, et al. The lacrimal gland in Sjögren's syndrome: can we unravel its mystery using ultrasound? Clin Exp Rheumatol. 2022;40(12):2428–2433. doi: 10.55563/clinexprheumatol/z1lzb1
17. Karagozoglu KH, Mahraoui A, Bot JCJ, et al. Intraoperative Visualization and treatment of salivary gland Dysfunction in Sjögren's syndrome patients using contrast-enhanced ultrasound sialendoscopy (CEUSS). J Clin Med. 2023;12(12):4152. doi: 10.3390/jcm12124152