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Mossel, Esther; Delli, Konstantina; van Nimwegen, Jolien F; Stel, Alja J; Haacke, Erlin A; Kroese, Frans G M; Spijkervet, Fred K L; Vissink, Arjan; Arends, Suzanne; Bootsma, Hendrika

Published in:
Annals of the Rheumatic Diseases

DOI:
[10.1136/annrheumdis-2017-212331](https://doi.org/10.1136/annrheumdis-2017-212331)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mossel, E., Delli, K., van Nimwegen, J. F., Stel, A. J., Haacke, E. A., Kroese, F. G. M., Spijkervet, F. K. L., Vissink, A., Arends, S., & Bootsma, H. (2018). The parotid gland connection: ultrasound and biopsies in primary Sjogren's syndrome. *Annals of the Rheumatic Diseases*, 77(7), [e38].
<https://doi.org/10.1136/annrheumdis-2017-212331>

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The parotid gland connection: ultrasound and biopsies in primary Sjögren's syndrome

We would like to thank Alegria *et al*¹ for their letter to the editor commenting on our recent publication entitled 'Ultrasonography of major salivary glands compared with parotid and labial gland biopsy and classification criteria in patients with clinically suspected primary Sjögren's syndrome'.² Our study was the first that directly compared the validity of ultrasound of major salivary glands (sUS) with parotid gland biopsy outcome. We showed that the agreement between sUS and parotid as well as labial gland biopsies was good but was slightly higher for the former.

As noted by Alegria *et al*,¹ we found different results for the positive predictive value (PPV) and negative predictive value (NPV) between sUS versus parotid and sUS versus labial gland biopsies.² Although these observations may indeed be caused by discordance between the parotid and labial gland biopsy outcome, there are other factors that may equally well contribute to this discrepancy. First, the parotid glands are assessed during the sUS examination and included in the scoring, whereas the labial glands are not.² Second, in 6%–15% of the general population, the labial gland biopsy is positive, while in only 5% of the general population, the parotid gland biopsy is positive.^{3–6} This implies that when biopsies of parotid and labial glands are taken simultaneously, at least up to 10% of the biopsies may be discordant. Third, the patient cohort in which sUS was compared with parotid gland biopsies was not exactly the same as the patient cohort in which sUS was compared with labial gland biopsies. However, when only taking into account the 43 patients who underwent both a parotid and labial gland biopsy, there still was a discrepancy between the predictive values of parotid and labial gland biopsies. In this group of 43 patients, compared with parotid gland biopsies, sUS showed a PPV of 64% (7/11) and NPV of 88% (28/32), and when compared with labial gland biopsies, PPV was 73% (11/15) and NPV was 75% (21/28).

Alegria *et al*¹ requested more information about the group of 43 patients who had both a parotid and labial gland biopsy, that is, the agreement between both biopsies and the correlation between sUS and the focus score in the parotid and labial gland biopsies. We fully agree with Alegria *et al*¹ that it is important

to make a direct comparison between parotid and labial salivary gland biopsies and not only to compare both to sUS. Such a detailed comparison of the results obtained with parotid and labial gland biopsies is currently in progress in a larger cohort of patients. In this study, the focus score of the parotid and labial gland biopsies will be compared, as suggested by Alegria *et al*, and the other histopathological characteristics of primary Sjögren's syndrome in both types of biopsies.

In the current study, in the 43 patients who underwent a double biopsy, the correlation between sUS and parotid gland focus score was $\rho=0.376$ (figure 1A), while the correlation between sUS and labial gland focus score was $\rho=0.412$ (figure 1B). Previously, Cornec *et al* reported a correlation of $\rho=0.61$ between sUS and focus score in labial salivary glands of participants in the TEARS trial.⁷ However, all patients in their cohort were already classified as primary Sjögren's syndrome according to the American European Consensus Group criteria, in contrast to our study, in which patients clinically suspected with p were included.^{7,8} This difference in patient selection could be the explanation for the discrepancy in reported correlation.

As Alegria *et al*¹ stated, Chisholm *et al*⁹ found that minor salivary gland biopsies have a greater specificity compared with major salivary gland biopsies. Whether this study is representative for current medical practice is discussable. First, Chisholm *et al*⁹ evaluated major salivary gland biopsies from the submandibular gland, whereas in our study,² parotid gland biopsies were evaluated. Whether the histopathology of the submandibular gland is similar to the parotid gland is unknown, since submandibular salivary glands are not easily accessible for taking incisional biopsies. Second, another important difference is that Chisholm *et al*⁹ performed a postmortem study. Thus, the study of Chisholm *et al*⁹ cannot be used as a direct comparison. On the other hand, two other studies showed that major salivary gland biopsies performed at least as well as minor salivary gland biopsies in the diagnosis of primary Sjögren's syndrome.^{6,10}

Currently, most groups still prefer to perform labial gland instead of parotid gland biopsies, as taking parotid gland biopsies requires specific surgical expertise.⁶ Therefore, labial gland biopsies are included in the various classification criteria sets and were the main focus of recent guidelines, regarding the histopathological evaluation of Sjögren's syndrome.^{8,11–13} However, there are several advantages of parotid gland biopsies

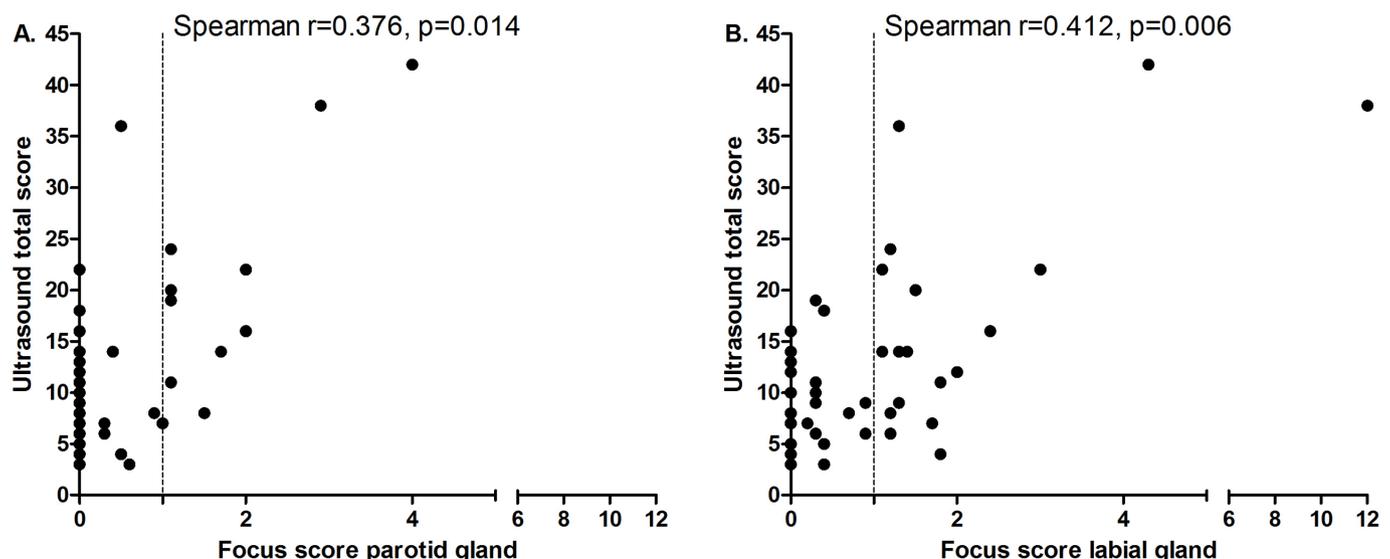


Figure 1 (A) Ultrasound total score compared with focus score in parotid gland biopsies. (B) Ultrasound total score compared with focus score in labial gland biopsies.



in comparison to labial gland biopsies, including the possibility of identifying mucosa-associated lymphoid tissue lymphoma at an earlier stage, the possibility of performing repeated biopsies of the same gland and allowing a direct gland-specific comparison with other diagnostic methods, like glandular specific saliva and ultrasound.^{6,14,15} Furthermore, in the study of Marx *et al.*,¹⁰ in five Sjögren's syndrome patients, a diagnosis of lymphoma was made based on the parotid gland biopsies, while the labial gland biopsies all lacked lymphomatous changes. Interestingly, we have shown that the baseline number of CD20⁺ B-cells/mm² of parenchyma could serve as a prognostic biomarker to predict rituximab response. Hence, baseline characteristics of the parotid gland biopsy might be our guide to personalised treatment.¹⁶

To conclude, the parotid gland should not be ignored and is an important organ in the evaluation of Sjögren's syndrome.

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Contributors The first manuscript was written by EM. All authors (KD, JFN, AJS, EAH, FG MK, FKLS, AV, SA and HB) critically reviewed the eLetter and approved the final version to be published.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

Data sharing statement There are no additional unpublished data.

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To cite Mossel E, Delli K, van Nimwegen JF, *et al.* *Ann Rheum Dis* 2018;**77**:e38.

Received 14 September 2017

Accepted 15 September 2017

Published Online First 29 September 2017

► <http://dx.doi.org/10.1136/annrheumdis-2017-212289>

Ann Rheum Dis 2018;**77**:e38. doi:10.1136/annrheumdis-2017-212331

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