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Parotid Gland Biopsy, the Alternative Way to Diagnose Sjögren Syndrome

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KEYWORDS

- Sjögren syndrome • Parotid gland • Labial gland • Salivary gland • Biopsy
- Diagnostics

KEY POINTS

- In Sjögren diagnostics, parotid gland incision biopsies can overcome most disadvantages of minor salivary gland excision biopsies.
- Sensitivity and specificity of parotid and minor salivary gland biopsies for diagnosing Sjögren syndrome are comparable.
- Lymphoepithelial lesions and early stage lymphomas are easier to detect in parotid gland tissue of patients with Sjögren syndrome.
- In contrast to minor salivary glands, repeated biopsies of the same parotid gland are possible, which is an important asset in monitoring disease progression as well as in studying the efficacy of treatment at a glandular tissue level.
- Histopathologic results from the parotid gland can be compared with other diagnostic results derived from the same gland (sialometry sialochemistry, sialography, scintigraphy, ultrasound, computed tomography, MRI).

INTRODUCTION

Salivary gland biopsy is a technique broadly applied in the diagnostic work-up of Sjögren syndrome (SS) as well as lymphoma accompanying SS, sarcoidosis, amyloidosis, and other connective tissue disorders. A focus score of 1 or greater per 4 mm² labial

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salivary gland tissue is considered as one of the 4 objective European-American Consensus Group classification criteria (AECG)¹ and one of the 3 objective American College of Rheumatology (ACR) provisional classification criteria² for SS. The focus scores reflect the number of infiltrates of 50 or greater mononuclear inflammatory cells, predominantly lymphocytes, in a perivascular or periductal location, typically adjacent to normal acini, per 4 mm² salivary gland tissue.^{3,4} Also in the under-construction consensus classification criteria of the European League against Rheumatism (EULAR) and ACR, a labial focus score of 1 or greater will be maintained as a leading classification criterion.⁵

Moreover, there are views that besides being of diagnostic value, labial salivary gland biopsies also may play a role in predicting lymphoma development⁶ as well as in monitoring disease and treatment efficacy.^{7–9} Recently, Fisher and colleagues¹⁰ reviewed the labial salivary gland pathologic changes that characterizes SS. They concluded that labial salivary gland biopsies offer a distinct potential as a biomarker in primary SS (pSS), particularly relevant to glandular involvement, and offer additional prognostic, stratification, and mechanistic insights. They also added that precise value of a labial salivary gland biopsy is yet hard to determine in the absence of proven immunomodulatory therapies in pSS and that further work on validation and understanding the natural history is needed.

In their review, Fisher and colleagues¹⁰ briefly mentioned parotid biopsies as an alternative to labial salivary gland biopsies but did not further state the advantages and disadvantages of parotid biopsies compared with labial salivary biopsies (Table 1).^{11,12} In this contribution, the authors discuss the potential of parotid salivary gland biopsies as an alternative way to diagnose SS and also with emphasis of its added value in lymphoma diagnostics and rating disease progression and treatment efficacy.

MINOR SALIVARY GLAND BIOPSY

Minor salivary glands are widely distributed in the labial, buccal, and palatal mucosa of the oral cavity. Because pathognomonic changes are seen in minor salivary glands, labial salivary gland biopsy is largely used for assisting the diagnosis of SS.^{4,13,14}

Surgical Considerations

Minor salivary glands, and labial salivary glands in particular, are easily accessible. The labial salivary glands lie above the muscle layer and branches of the mental nerve (labial sensory nerves) and are separated from the oral mucous membrane by a thin layer of fibrous connective tissue. Although the chance of excessive bleeding is minimal because the arterial supply to the lip lies deep, there is a serious hazard of sensory nerve injury, as the labial sensory nerves are closely associated to the minor salivary glands (Fig. 1).

Chisholm and Mason³ introduced labial salivary gland biopsies in the diagnosis of SS.³ The biopsies involve oral preparation of patients with local anesthetic infiltration followed by excising an ellipse of oral mucous membrane down to the muscle layer. The wound was closed with 4-0-gauge silk sutures, which were removed after 4 to 5 days. Ideally 6 to 8 minor glands are harvested and sent for histopathologic examination.

Several clinicians have revised the Chisholm and Mason technique. Currently, the approach of Greenspan and colleagues¹³ and Daniels¹⁴ is mostly applied (Fig. 2). This approach is described in detail on the Sjögren's International Collaborative Clinical Alliance Web site.¹⁵ In short, the biopsy has to be performed through the mucosa of the lower lip that appears normal clinically. After applying local anesthetics, the lip is everted to expose the mucosa. Next, a 1.0- to 1.5-cm horizontal incision will be made to the right or left of the midline, approximately halfway between the vestibule and the

vermillion border and halfway between the midline and the labial commissure. The lamina propria is bluntly dissected to release the minor salivary glands from the lamina propria beyond the incision and to bring them into the operating field. Approximately 7 minor salivary glands should be removed to provide a minimum gland section area of 8 to 12 mm² for microscopic focus scoring.¹⁰ Finally, the mucosal incision margins are repositioned and sutured with 5-0 rapid absorbable (polyglactin/L-lactide acid) sutures (see Fig. 2).

Histologic Grading

The first grading system for salivary gland biopsies was used by Chisholm and Mason³ in an attempt to standardize the examined area and record the degree of histopathologic change. At present, according to the revised AECG and provisional ACR classification criteria for SS (and also in the recent ACR-EULAR classification under construction), a labial salivary gland biopsy is considered positive if the glands (obtained through normal-appearing mucosa) demonstrate focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score of 1 or greater (Fig. 3). Diagnosis of nonspecific chronic sialadenitis, sclerosing chronic sialadenitis, and granulomatous inflammation need to be excluded. A sufficient area of labial salivary gland tissue has to be examined, as Al-Hashimi and colleagues¹⁶ showed that focus score might differ on multiple sections taken from the same labial glands specimen.

Complications

Complications of labial salivary gland biopsies include localized (permanent) sensory alteration of the lip, external hematoma, local swelling, formation of granulomas, internal scarring and cheloid formation, failing sutures, and local pain.^{11,13,14,17–24} The localized sensory alterations are frequently described with the terms *anesthesia*, *reduced or partial loss of sensation*, *transitory numbness*, and *hypoesthesia*. These localized sensory alterations of the vermillion border of the lower lip mucosa may last for a few months but can be permanent in up to 10%, which should be considered as relatively high for a diagnostic procedure.^{11,18}

PAROTID GLAND BIOPSY

The parotid gland is divided into a superficial and deep lobe based on the course of the facial nerve as it passes through (see Fig. 1). The technique of the parotid gland biopsy was initially described by Kraaijenhagen²⁵ and modified by Pijpe and colleagues¹¹ (Fig. 4). The parotid biopsy is performed in the superficial lobe area where the facial nerve is 1.5 to 2 cm below the surface of the gland.

Surgical Considerations

In short, the area in the region of the earlobe is anesthetized (auriculotemporal nerve) with 0.5 mL local infiltration anesthesia followed by skin disinfection and standard preparation. With a No. 15 knife-blade, a small 1- to 2-cm incision is made just below the earlobe near the posterior border of the mandible. The skin is incised; after blunt dissection of the subdermal tissue, the parotid capsule is exposed, followed by carefully opening the capsule and excision of the required amount of superficial parotid gland tissue for histopathologic review. The capsule of the parotid gland and subcutaneous layer is closed with 5-0 absorbable (polyglycolic acid) sutures, whereas the skin is closed with 5-0 nylon sutures (see Fig. 4). With this surgical approach, there are no reports of development of sialoceles or fistula. For details see the instructional film.

Table 1

Techniques to perform a labial or parotid salivary gland biopsy

	Technique	Advantages	Complications
<i>Labial gland</i>			
Chisholm & Mason, ³ 1968	Ellipse of oral mucous membrane down to the muscle layer; harvest of 6–8 glands; wound closure with 4-0 silk sutures, which must be removed after 4–5 d	<ul style="list-style-type: none"> • Widely distributed glands • Easily accessible glands • Minimal chance of bleeding • Can identify germinal center–like structures 	<ul style="list-style-type: none"> • Localized, 6%–10% permanent, sensory alteration of the lips and skin in the mental region • Internal scarring and cheloid formation • Suture failing
Greenspan et al, ¹³ 1974	1.5–2.0 cm linear incision of mucosa, parallel to the vermillion border and lateral to the midline		
Marx et al, ¹⁸ 1988	Mucosal incision of 3.0 × 0.75 cm		
Delgado & Mosqueda, ¹⁹ 1989	Longitudinal incision of 1 cm in the labial mucosa in front of the mandibular cuspids		
Guevara-Gutierrez et al, ⁵⁸ 2001	Punch biopsy		
Mahlstedt et al, ²⁰ 2002	1.0- to 1.5-cm wedge-shaped incision between the midline and commissure		
Gorson & Ropper, ⁵⁹ 2003	1-cm vertical incision just behind the wet line through the mucosa and submucosa		
Berquin et al, ²¹ 2006	Oblique incision, starting 1.5 cm from the midline and proceeding latero-inferiorly, avoiding the glandular free zone in the center of the lower lip		
Caporali et al, ²² 2007	Small incision of 2–3 mm on the inner surface of the lower lip		

*Parotid gland*Kraaijenhagen,²⁵ 1975Marx et al,¹⁸ 1988McGuirt et al,⁶⁰ 2002Baurmash,⁶¹ 2005Pijpe et al,¹¹ 2007

1- to 2-cm incision just below and behind the earlobe near the posterior angle of the mandible; skin is incised and the parotid capsule exposed by blunt dissection capsule of the gland opened and adequate amount of superficial parotid tissue removed, approximately 5 × 5 mm; procedure completed with a 2- to 3-layered closure

Adam et al,⁶² 1992Berquin et al,²¹ 2006

Mucosal incision 1 cm anterolaterally from the Wharton duct to 1 cm anteroposterior; blunt dissection and harvest of 0.5 cm³ of glandular tissue; wound edges joined with 1–2 resorbable stiches

- Presence of germinal centers
- Presence of LELs
- (Early) identification of MALT
- Can repeatedly harvest same gland
- Direct comparison with other diagnostic results derived from the same gland (eg, secretory function, sialography, scintigraphy, ultrasound)

- Temporary change in sensory sensation of the skin in the area of the incision
- More demanding surgical expertise

Abbreviations: LELs, lymphoepithelial lesions; MALT, mucosa-associated lymphoid tissue.

Adapted from Delli K, Haacke EA, Pollard RP, et al. Baseline characteristics of parotid gland histopathology predict responsiveness of patients with primary Sjögren's syndrome to rituximab treatment. *Scand J Immunol* 2015;81(5):434–5.

Fig. 1. Association of the labial and parotid salivary glands with, respectively, the mental and facial nerve. (A) The mental nerve (*) has 3 branches: one branch supplying the skin of the chin and 2 branches supplying the skin and mucous membrane of the lower lip. The branch that supplies the mucous membrane usually has 2 sub-branches of which the vertical one has an ascending course toward the vermilion border and is in close relation to the labial salivary glands (**). (B) The facial nerve enters the parotid gland forming a characteristic branching pattern that resembles a goose foot and is known as the pes anserinus. The parotid gland is divided into a superficial and deep lobe based on the course of the facial nerve as it passes through. In the area of the incisional biopsy of the parotid gland, the distance between the surface of the parotid gland and the facial nerve is approximately 1.5 to 2.0 cm. (From Delli K, Vissink A, Spijkervet FK. Salivary gland biopsy for Sjögren's syndrome. *Oral Maxillofac Surg Clin North Am* 2014;26(1):23–33; with permission.)

Fig. 2. Technique for harvesting labial salivary glands after infiltration of local anesthesia. (A) A horizontal incision of approximately 1.0 to 1.5 cm is made on the mucosal site of the lip. Just the epithelium is incised. (B) About 6 to 8 labial salivary glands are harvested avoiding damage to the branches of the mental nerve. (C) Wound closure with 5-0 rapid absorbable (polyglactin/L-lactide acid) sutures; inverted buried notches.

Fig. 3. Histopathology of the labial salivary glands of a patient with SS, which is characterized by lymphocytic infiltration (*asterisk*) of the excretory ducts and destruction of the acini, fulfilling the criterion of a focus score of 1 or greater (hematoxylin-eosin, original magnification $\times 10$).

Histologic Grading

Pijpe and colleagues¹¹ established a new set of validated histopathologic criteria for diagnosing SS in accordance with the AECG classification criteria based on biopsy of the parotid gland (**Fig. 5**). A parotid biopsy is considered positive when it has a focus

Fig. 4. Technique of a parotid biopsy. (A) The skin below the ear lobe is infiltrated with local anesthesia. (B) With a No. 15 blade a small 1- to 2-cm incision is made just below and behind the earlobe near the posterior border of the ascending ramus of the mandible. (C) The parotid capsule is exposed by blunt dissection after the skin incision. The capsule of the gland is carefully opened and a small amount of $5 \times 5 \times 5$ -mm superficial parotid tissue is removed. (D) The procedure is completed with a 2- to 3-layered closure with 4-0-gauge absorbable sutures (polyglycolic acid), while the skin layer is closed with 5-0 nylon sutures.

Fig. 5. Histopathology of the parotid salivary glands of a patient with SS. (A) Foci. (B) Lymphoepithelial lesions (H&E).

score of 1 or greater, defined as the number of lymphocytic foci (which are adjacent to normal-appearing acini and contain >50 lymphocytes) per 4 mm^2 of glandular parotid tissue (including fat tissue; see Fig. 5A), irrespective of the presence of benign lymphoepithelial lesions (LELs; see Fig. 5B). LELs are a characteristic histologic feature of the salivary, predominantly parotid, glands of patients with SS. LELs form through basal cell hyperplasia forming a multilayered epithelium. Between these reactive ductal epithelial cells, lymphocytes are present.

Complications

Potential complications of parotid salivary gland biopsies include the development of sialoceles and salivary fistulae and a temporary change in sensation in the skin area of the incision,^{11,18} which are obvious because of the surgical opening of the skin and superficial gland area. As mentioned before, development of sialoceles or fistula has not yet been observed by the authors and is not reported in the literature. The often-mentioned potential risk of facial nerve damage is based on the lack knowledge of anatomic and surgical skills as this nerve, as also mentioned before, is 1.5 to 2.0 cm below the surface of the gland. The only reported complications are a temporary change in sensation in the skin area of the incision. No permanent complications are, however, documented in the literature.^{11,18,26} The level of postoperative pain accompanying a parotid gland biopsy is comparable with a lip biopsy.¹¹

SUITABILITY OF SALIVARY GLAND BIOPSIES

Diagnostic

As mentioned before, a labial salivary gland biopsy is considered as positive for SS when focal lymphocytic sialadenitis with a focus score of 1 or greater per 4 mm^2 glandular tissue is present (see Fig. 3). However, for proper interpretation of the biopsy specimens broad experience is needed as focal lymphocytic sialadenitis may occur in conjunction with other autoimmune diseases and even in healthy subjects, in particular in the elderly.²⁷ Typically for pSS, the lymphocytic foci have to be adjacent to normal-appearing mucous acini and contain no more than a minority proportion of plasma cells. Furthermore, at greater than a focus score of 10, foci are typically confluent; an arbitrary score of 12 is often applied for such biopsies.^{13,14} Other difficulties that may interfere with the interpretation of the biopsies are features more usually associated with nonspecific chronic sialadenitis, such as acinar atrophy, interstitial

fibrosis, and duct dilatation. These features are relatively common and increase with age and may also coexist with pSS-related focal lymphocytic sialadenitis.^{10,28} Replacement of glandular tissue with fibrotic tissue as a result of age and chronic salivary gland inflammation may lower the focus score and lead to a burnt-out appearance.^{10,29} Moreover, it may be difficult to harvest a sufficient number of labial salivary glands in atrophic submucosa of patients with long-standing SS.³⁰

In contrast to labial glands, parotid salivary biopsies allow the clinician to monitor disease progression and to assess the effect of an intervention treatment in SS. This assessment is feasible because parotid tissue can be harvested relative easily, repeated biopsies from the same parotid gland are possible, and the histopathologic results can be compared with other diagnostic results derived from the same gland (eg, secretory function, sialographic appearance, scintigraphy, ultrasound, computed tomography [CT], MRI).³¹ Additionally, by performing parotid biopsies as a routine diagnostic procedure for SS, LELs and lymphomas located in the parotid gland can be identified (see section on lymphoma).^{18,32} So, the question remains as to what biopsy should be preferred for diagnostics and/or monitoring disease progression and treatment efficacy.

Disease Progression

There are only few studies that compared the diagnostic characteristics of major and minor salivary gland biopsies and even none that compared the ability of both biopsy types to monitor disease progression and treatment efficacy. Pijpe and colleagues¹¹ compared the diagnostic ability of labial and parotid salivary gland biopsies in diagnosing pSS as well as compared their morbidity. They showed that the diagnostic sensitivity and specificity were identical. Moreover, the presence of characteristic benign LELs in the parotid gland can aid the diagnosis of SS. The observation that LELs are commonly present in parotid biopsies and are virtually absent in labial salivary gland biopsies was earlier confirmed by Pennec and colleagues³³ and Carbone and colleagues.³⁴ The incidence of germinal centers in the major and minor salivary gland biopsies is comparable.¹¹ There is a need for larger studies comparing the diagnostic utility of labial and parotid salivary gland biopsies in the diagnostic work-up of SS emphasizing whether these procedures are exchangeable or that a specific biopsy type is preferred for a specific diagnostic issue regarding SS or SS-associated diseases.

Treatment Evaluation Purposes

EULAR has developed a disease activity index (EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI]) and a patient-reported index (EULAR Sjögren's Syndrome Patient Reported Index [ESSPRI]) as validated outcome measures for SS.^{35–38} Although the development is an important advantage, ESSDAI focuses on systemic disease features and is so less relevant to patients with predominantly glandular features. The ESSPRI addresses the symptomatic components of dryness, pain, and fatigue. Fatigue has an important impact on the quality of life but might be susceptible to placebo effects or the impact of concomitant disorders leading to important implications for sample size. Thus, as posed by Fisher and colleagues,¹⁰ an objective biomarker of glandular inflammation would, therefore, be desirable; salivary gland biopsy has the added advantage that it may offer insights into the mechanism of action of a novel agent or, more importantly, reasons for failure in a negative study.

When comparing the potential application of labial and parotid salivary gland biopsies with regard to disease activity and progression, studies involving repeated labial salivary gland biopsies revealed that in patients presenting with sicca

symptoms, a focus score of 1 or greater was associated with antibodies to Ro and La, rheumatoid factor, antinuclear antibody, and a lower unstimulated whole salivary flow rate.^{4,39,40} It was also shown that a higher focus score is accompanied by a larger decrease in an unstimulated⁴¹ and stimulated⁴² whole salivary flow rate over time. Repeated labial salivary gland biopsies might have some value in assessing the effect of biologicals on the glandular level as labial salivary gland biopsies seems to be of added value in rating the efficacy of treatment with rituximab,⁷ abatacept,⁸ or belimumab.⁹ It has to be mentioned, however, that the same labial salivary glands are not examined as a function of time but a new sample of glands collected from the same patient bringing the hazard of the reproducibility of, for example, a focus score in repeated sections from even the same labial salivary glands into mind.¹⁶ However, Kapsogeorgou and colleagues⁴³ showed that the infiltration grade and prevalence of the major infiltrating cell types (T and B cells, macrophages, dendritic cells, natural killer cells) remained largely unchanged during a median 55-month biopsy time interval follow-up (quartiles 42–81) indicating that the labial salivary gland histopathology is rather stable with time and probably does not readily reflect disease progression and/or disease activity.

In contrast to labial salivary glands, repeated biopsies from the same parotid gland are possible, which is probably an important asset in studies assessing the efficacy of a treatment in patients with SS or monitoring disease progression. Another important advantage is that the histopathologic results can be compared with other diagnostic results derived from the same gland (secretory function, sialographic appearance, scintigraphy, ultrasound, CT, MRI). Moreover, as mentioned before, LELs are often observed in parotid gland tissue of patients with SS and rarely in labial salivary gland tissue. These LELs, a characteristic histologic feature of the major salivary glands in SS,⁴⁴ develop as a result of basal cell hyperplasia forming a multi-layered epithelium. Between these reactive ductal epithelial cells, lymphocytes are present.⁴⁴

Although features of labial salivary gland pathology have been associated with a variety of serologic, clinical, and imaging parameters, features of parotid salivary gland tissue are not yet associated with such parameters. However, currently several studies are underway assessing whether histopathologic features reflect changes in whole and glandular salivary flow, serum, and salivary gland ultrasonography. First results will become available shortly indicating whether disease progression and disease activity are indeed accompanied by characteristic features at the level of parotid gland histopathology. With regard to parotid salivary gland tissue as a monitor of treatment efficacy, more progress has been made. Pijpe and colleagues³¹ showed in an open-label trial that sequential parotid biopsy specimens obtained from patients with pSS before and after rituximab treatment demonstrated histopathologic evidence of reduced glandular inflammation and redifferentiation of lymphoepithelial duct lesions to regular striated ducts as a putative morphologic correlate of increased parotid flow and normalization of the salivary sodium content. Next, Delli and colleagues⁴⁵ assessed the prognostic value of parotid gland immunopathology with regard to responsiveness of patients with pSS to rituximab treatment in a randomized placebo-controlled study. These investigators found a significant reduction in the number of CD20+ B cells per square millimeter of parenchyma, whereas no reduction was observed in placebo-treated patients. Furthermore, the relative number and severity of LELs and germinal centers significantly reduced after rituximab treatment. Moreover, when comparing the baseline characteristics of clinical responders with nonresponders to rituximab treatment, the number of CD20+ B cells per square millimeter of parenchyma was significantly higher in responders, which

might predict the responsiveness of patients with pSS to rituximab treatment. In addition, an open-label study with abatacept⁴⁶ showed that treatment did not affect the focus score, area of lymphocytic infiltrate, and number of LELs infiltrating B and T cells. However, abatacept reduced the presence of germinal centers (GC), which was associated with an improvement in the glandular domain (reduction in swelling) of the ESSDAI. Thus, abatacept seems to inhibit local T-cell dependent B-cell activation in parotid gland tissue of patients with pSS as witnessed by the decline in GC per square millimeter after treatment. Furthermore, the presence of GC at baseline predicts response in ESSDAI glandular domain after abatacept treatment. These observations have to be confirmed in a placebo-controlled study, a study that is currently in progress.

SALIVARY GLAND BIOPSIES AND LYMPHOMAS

Five percent to 10% of patients with SS develop malignant B-cell lymphoma,^{47–49} 48% to 75% of which are of the mucosa-associated lymphoid tissue (MALT)-type. These MALT B-cell lymphomas are most frequently located in the parotid gland.^{50–52} Theander and colleagues⁶ suggested that the presence of GC-like structures in pSS diagnostic labial salivary biopsies is highly predictive and an easy-to-obtain marker for non-Hodgkin lymphoma development. They even posed that presence of these GC-like structures allows for risk stratification of patients and the possibility to initiate preventive B-cell-directed therapy. Later on, however, Johnsen and colleagues⁵³ were unable to detect a clear association between cellular infiltrates, B-cell clonality, and lymphoma development in labial salivary gland biopsies. The authors' recent data indicate that presence of germinal centers in diagnostic (labial) biopsies is not a risk factor for the development of MALT lymphoma in the parotid glands.⁵⁴ Because lymphomas in patients with pSS mainly develop in parotid glands, taking parotid gland biopsies may be a great asset in both diagnosing pSS-associated lymphomas as well as in titrating which therapy is needed.³² Quintana and colleagues⁵⁵ and De Vita and colleagues⁵⁶ mentioned that LELs and reactive lymphoid follicles, features that are commonplace in parotid salivary gland pathology of patients with pSS, indicate malignant lymphoma and, thus, benign LELs must be discriminated from premalignant lesions. Haacke and colleagues⁵⁴ looked with more detail into salivary gland biopsies of patients with pSS with regard to LELs and observed that FcRL4⁺ B cells are in close association with LELs and that these FcRL4⁺ B cells are significantly increased when comparing the parotid gland with the labial gland. As MALT lymphomas, and a small subset of diffuse B-cell lymphomas, express FcRL4,⁵⁷ this observation might explain why lymphomas in patients with pSS commonly develop in parotid and not in minor salivary glands and, thus, favors taking a parotid and not a labial salivary gland biopsy in the diagnostic work-up of patients with SS, at least in patients with a suspect of lymphoma development.

SUMMARY

Early diagnosis and objective treatment evaluation of costly therapies based on biologicals are of high importance in SS. Unfortunately, so far there is not a single test capable of confirming the diagnosis of SS. A positive salivary gland biopsy is strong evidence, which in correlation with additional diagnostic tests can establish a definite conclusion. Parotid gland biopsy is a relatively simple technique with no permanent morbidity reported compared with a relative high morbidity rate of labial salivary gland biopsies due to the rather high hazard of permanent damage to the sensory nerve

supply of the lower lip in the latter biopsies. Parotid biopsies are able to overcome most of these disadvantages.

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