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Utility of navigation system-guided submandibular gland core needle biopsy in the diagnosis of immunoglobulin G4-related sialadenitis

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Abstract. Pathological diagnosis is important for the definite diagnosis of immunoglobulin G4-related sialadenitis (IgG4-RS). Core needle biopsy (CNB) is a scarless technique; however the pathological heterogeneity of IgG4-RS (a particular feature of this disease) could be the potential cause of the inferior diagnostic capability of submandibular gland CNB (SMG-CNB) for IgG4-RS. The aim of this study was to explore technical improvements in SMG-CNB and improve its diagnostic power in IgG4-RS diagnosis. Eighteen patients clinically suspected for IgG4-RS were enrolled and underwent both SMG-CNB and SMG surgical biopsy. A navigation system (Brainlab) was employed during SMG-CNB to obtain representative samples and avoid blood vessel injury. Histopathological and immunopathological findings for the SMG-CNB samples were in good concordance with SMG surgical biopsy. There was no statistically significant difference between SMG-CNB and SMG surgical biopsy in IgG-positive cell count (132.4 ± 59.3 vs 132.2 ± 47.5, $P = 0.99$), IgG4-positive cell count (102.2 ± 39.7 vs 97.2 ± 27.6, $P = 0.67$), or IgG4-positive/IgG-positive cell count ratio (78.6% ± 0.1% vs 75.2% ± 0.1%, $P = 0.29$). A moderate or strong significant correlation was found between SMG-CNB and SMG surgical biopsy for these cell counts and ratio (all $P < 0.01$). The diagnostic consistency of SMG-CNB and SMG surgical biopsy was 100%. The Brainlab navigation system may assist in collecting representative SMG-CNB samples from typical pathological lesions. Tissues obtained from SMG-CNB are sufficient for the pathological diagnosis of IgG4-RS. Standardized SMG-CNB is expected to replace SMG surgical biopsy for IgG4-RS diagnosis.

Keywords: Immunoglobulin G4-related disease; Sialadenitis; Diagnosis; Large-core needle biopsy; Surgical navigation system.

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Immunoglobulin G4-related sialadenitis (IgG4-RS) is a subclass of immunoglobulin G4-related disease (IgG4-RD). It is a newly recognized immune-associated disease entity characterized by enlargement of the major salivary glands, dense IgG4-positive lymphoplasmacytic infiltration, storiform fibrosis, and an elevated serum IgG4 concentration.[1,2]

The clinical diagnosis of IgG4-RS requires the fulfilment of comprehensive diagnostic criteria, including clinical, serological, radiological, and pathological features. These criteria were established in 2011[3] and further updated in 2019.[4] As the histopathological and immunopathological characteristics are the decisive evidence for a definite diagnosis of IgG4-RS,[5] a biopsy is generally recommended.

The submandibular gland (SMG) is the most frequently involved major salivary gland, and SMG surgical biopsy is the most common and reliable means of IgG4-RS diagnosis.[6] However, this method leaves cervical scars and has the potential to lead to facial nerve injury. Labial salivary gland (LSG) biopsy, a relatively minimally invasive technique that effectively contributes to the diagnosis of Sjögren's syndrome,[7] has been proposed to assist in IgG4-RS diagnosis. However, recent studies have revealed insufficient diagnostic accuracy and sensitivity for LSG biopsy, due to the uncertainty of histopathological and immunohistochemical changes in the LSG.[6,8–13]

With its advantages of a scarless intervention and minimally invasive technique, core needle biopsy (CNB) has recently been applied extensively in clinical practice. Moreover, the application of CNB in the diagnosis of IgG4-RD has also been reported.[14–16] However, submandibular gland core needle biopsy (SMG-CNB) has been reported to have inferior diagnostic capability.[6,14,16]

A particular feature of IgG4-RS is its pathological heterogeneity, and the severity of pathological changes within a single salivary gland varies from lobule to lobule.[2,17] The present authors hypothesized that this pathological feature of IgG4-RS could be the potential cause of the inferior diagnostic capability of SMG-CNB reported previously. Thus, obtaining typical samples from seriously diseased lesions might contribute to the diagnostic accuracy of SMG-CNB. Whether typical pathological tissues can be obtained by SMG-CNB and whether the tissues from SMG-CNB are sufficient for histopathological and immunopathological identification needs to be explored further. The aims of this study were (1) to explore technical improvements in SMG-CNB; (2) to improve the diagnostic power of SMG-CNB in IgG4-RS diagnosis; and (3) to verify whether SMG surgical biopsy could be replaced by SMG-CNB in IgG4-RS diagnosis.

Materials and methods

Patients

Eighteen patients suspected of having IgG4-RS were enrolled in this study at Peking University School of Stomatology, between September 2020 and July 2022. These patients underwent both SMG-CNB and SMG surgical biopsy in the same session. Ten of the patients were female and eight were male (female to male ratio 1.25:1); their median age was 57.7 years (range 31–74 years).

The inclusion and exclusion criteria were defined according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) comprehensive diagnostic criteria.[4] In brief, the inclusion criteria applied in this study were (1) unilateral or bilateral swelling of the submandibular gland with or without swelling of multiple exocrine glands (lacrimal, parotid, and sublingual glands) that had lasted > 3 months; (2) serum IgG4 concentration > 140 mg/dl; (3) radiological findings suspicious for IgG4-RS. Patients who met the following exclusion criteria were excluded: radiologically suspicious for malignancy or infection; recurrent fever; leukopenia, thrombocytopenia, or eosinophilia found on serology; or met other ACR/EULAR exclusion criteria.

Ethical approval for this study was obtained from the Ethics Committee for Human Experiments of Peking University School of Stomatology (Protocol Approval PKUSS-IRB-202059178) and all patients provided written informed consent prior to participation.

Navigation system preparation

Considering the pathological heterogeneity of IgG4-RS within a single gland, the aim was to collect samples from the superficial lobules of the SMG, where the pathological change is generally more severe.[17] It was also sought to avoid the blood vessels surrounding the SMG and the branches extending into the gland in order to prevent accidental injury. In this study, SMG-CNB was assisted with the Brainlab navigation system (Brainlab, Munich, Germany).

Before surgery, all patients underwent a contrast-enhanced computed tomography (CT) scan. The CT data in DICOM format were imported into iPlan CMF 3.0 software (Brainlab) to create the navigation plan. The navigation plan consisted of a three-dimensional reconstruction of the skin and bones of the head and neck region and volume reconstruction of the enlarged SMG; the biopsy needle trajectory, blood vessels adjacent to the SMG (facial artery and facial vein in particular), and the blood vessel branches extending into the gland were outlined (Fig. 1A). The entire needle trajectory was limited to the superficial lobules of the SMG in order to obtain representative tissue. Moreover, the needle trajectory was designed to be at a distance of at least 5 mm from the blood vessels.

Before surgery, the navigation platform was set up in the operation room. The reference frames mounted with three location spheres were respectively fixed on the patient's head, the surgical probe, and the biopsy needle. After proceeding with the navigation registration, the pre-designed navigation plan was displayed on the computer screen, and the real-time needle trajectory was also shown.

Navigation system-guided SMG core needle biopsy

A 14-gauge Bard Magnum biopsy needle with Bard Magnum biopsy instrument (C R Bard Inc., Tempe, AZ, USA) was used for the SMG-CNB. The length of the sample notch was 19 mm, and the sampling depth was set at 22 mm. The patient was placed in the supine position, with hyperextension of the neck and the head turned to the opposite side from the side that was biopsied. The affected side was disinfected, and 1% lidocaine local infiltration anaesthesia was administered. With the assistance of the navigation system, the needle entry point, puncture direction, and surface projection of the enlarged SMG were marked on the skin, as shown in Fig. 1B. The needle path was corrected in real time

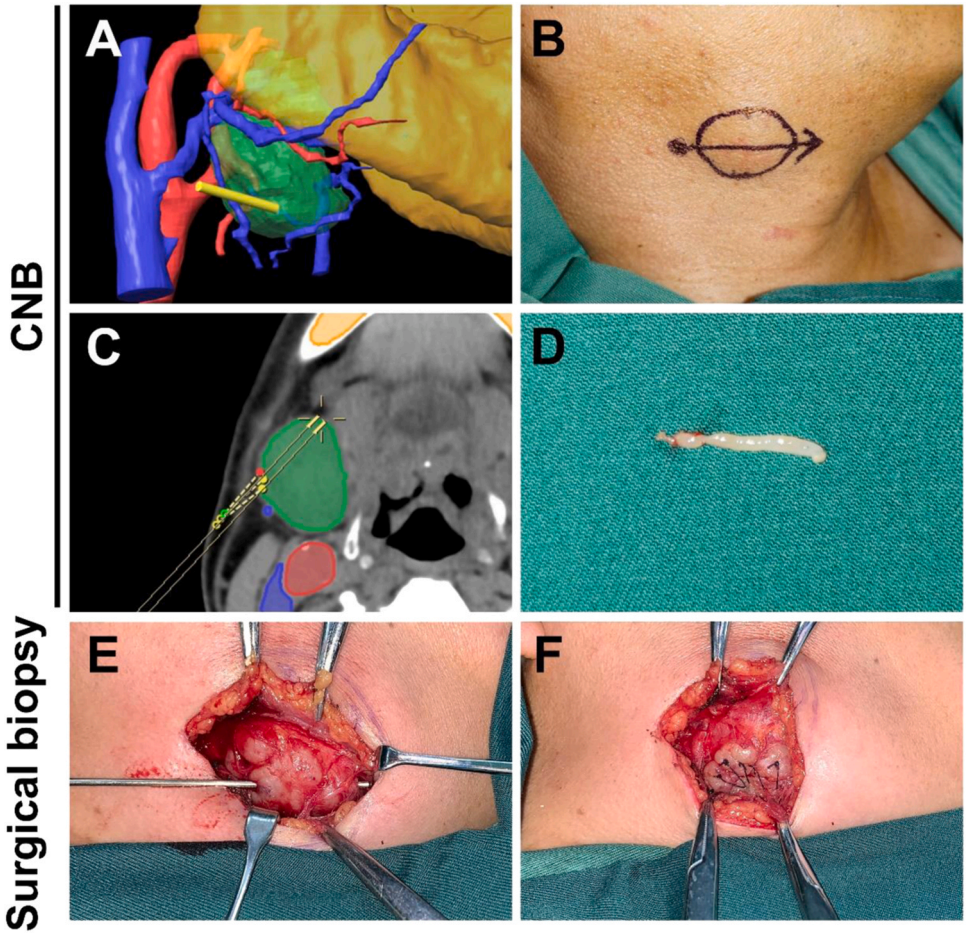

Fig. 1. Surgical procedures of SMG-CNB (A–D) and SMG surgical biopsy (E, F). (A) Preoperative navigation plan. (B) The needle entry point, puncture direction, and surface projection of the enlarged SMG were marked on the skin with the assistance of the navigation system. (C) The biopsy needle arriving at the pre-planned position with real-time guidance. (D) Core tissue retrieved from the SMG-CNB. (E) The path of the previous CNB was identified during the surgical biopsy, and the biopsy specimen was obtained adjacent to this path. (F) The SMG was sutured after sampling. SMG, submandibular gland; CNB, core needle biopsy.

according to the pre-planned needle trajectory (Fig. 1C). Only one tissue core was taken in each case (Fig. 1D). The collected tissue was immediately immersed in paraformaldehyde and sent for histopathological and immunohistochemical examination. The submandibular region was temporarily compressed with gauze and a surgical biopsy was then performed.

SMG surgical biopsy

The SMG surgical biopsy was performed immediately after SMG-CNB. A submandibular incision was made, and the marginal mandibular branch of the facial nerve was protected. The submandibular gland was exposed and the previous path of the CNB needle was identified, as shown in Fig. 1E. A tissue section of approximately $5 \times 8 \times 8\ mm^3$ right by the CNB needle path was then bluntly separated along the lobules and was sectioned using a lobular unit, as described previously.[8] Forced clamping of the tissues was avoided during the operation. The SMG was sutured after sampling, and the wound was closed (Fig. 1F). The collected sample was immediately immersed in paraformaldehyde and sent for histopathological and immunohistochemical examination.

Histopathological and immunohistochemical evaluation

For the histopathological evaluation, haematoxylin–eosin staining was performed as described previously.[8] The degree of acini atrophy and stromal fibrosis, the severity of inflammatory cell infiltration, size of lymphoid follicles with or without germinal centres, presence of obliterative phlebitis, and eosinophil infiltration were analysed under an optical microscope (Leica, Heidelberg, Germany). The severity of inflammation and fibrosis was classified into three stages according to the modified Seifert classification.[2]

For the immunochemical evaluation, immunohistochemistry was performed as detailed previously.[8] Briefly, 5-μm sections were dewaxed and rehydrated, and subjected to heat-induced antigen retrieval. After blocking in 3% hydrogen peroxide and 10% goat serum for 20 min, the slices were incubated with primary IgG antibodies (ZA-0448; ZSGB-BIO, Beijing, China), IgG4 antibodies (ZA-0576; ZSGB-BIO), and CD21 antibodies (ab237981; Abcam, Cambridge, UK) overnight at 4 °C. After incubation with secondary antibody, the antibody binding was detected using a diaminobenzidine substrate kit (Dako, Agilent

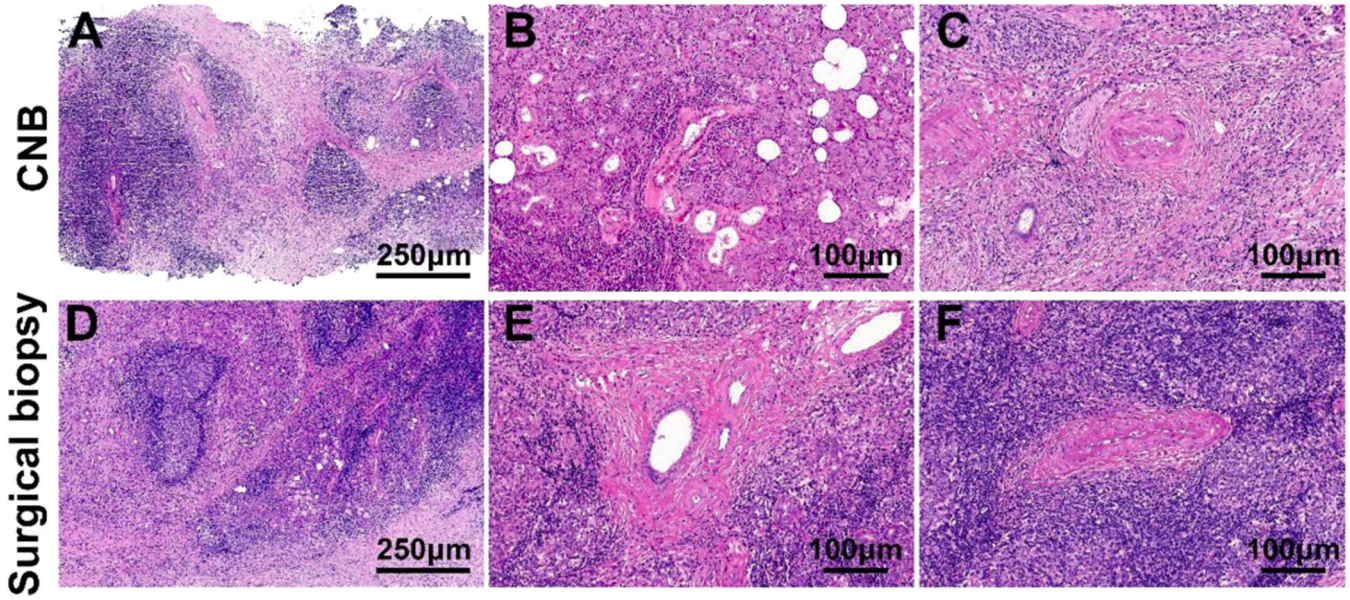

Fig. 2. Histopathological characteristics of the submandibular gland in IgG4-RS patients: SMG-CNB samples (A–C); SMG surgical biopsy samples (D–F). (A) (D) show storiform fibrosis, lymphoplasmacytic infiltration, and lymphoid follicle formation; (B) (E) show periductal collagen sheath; (C) (F) show obliterative phlebitis. SMG, submandibular gland; CNB, core needle biopsy.

Technologies Company, Carpinteria, CA, USA). Three images (high-power fields, 10 × 40) of each species were photographed using an optical microscope and analysed by two independent pathologists who were blinded to the sample information. In the case of disagreement, a third pathologist was consulted.

Statistical analysis

All data are presented as the mean ± standard deviation. The data analysis was performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). The statistical data were analysed with the independent *t*-test and Pearson correlation analysis. $P < 0.05$ was considered statistically significant.

Results

Serological findings

All 18 patients showed typical serological changes, with high levels of serum IgG (mean 2187.4 ± 726.0 mg/dl) and serum IgG4 (mean 877.4 ± 749.3 mg/dl).

Navigation-guided SMG core needle biopsy

All 18 patients enrolled in this study underwent SMG-CNB, and sufficient high-quality tissues were harvested. A second CNB was performed in one patient as no tissue was obtained the first time. The length of the CNB tissue obtained ranged from 12 mm to 19 mm (mean 16.0 ± 2.7 mm); the volume ranged from 24 mm^3 to 38 mm^3 (mean 32.0 ± 5.3 mm^3). All of the sampled tissues from SMG-CNB were subjected to histopathological and immunopathological evaluation, and all were independently diagnosed as IgG4-RS by two pathologists.

All 18 samples from SMG-CNB presented typical histopathological features such as storiform fibrosis, acini atrophy, lymphoplasmacytic infiltration, and lymphoid follicle formation with map-shaped germinal centres (Fig. 2A–C). The periductal collagen sheath was observed in all 18 samples (100%), and obliterative phlebitis was observed in 15 of the 18 samples (83.3%). Regarding the histopathological classification, one sample was classified as stage 1, seven as stage 2, and 10 as stage 3.

Immunohistochemistry showed the infiltration of a large number of IgG-positive and IgG4-positive lymphoplasmacytic cells in all SMG-CNB samples (Fig. 3A). The average number of IgG-positive plasma cells was 132.4 ± 59.3 per high-power field, the average number of IgG4-positive plasma cells was 102.2 ± 39.7 per high-power field, and the average ratio of IgG4-positive/IgG-positive plasma cells was 78.6% ± 0.1% (Supplementary Material Table S1). Lymphoid follicle formation was further confirmed by numerous CD21 stained follicular dendritic cells.

The SMG-CNB procedure was well tolerated by all patients. No facial artery or facial vein injury occurred during the CNB operation. A transient complication was noticed in one case: localized haematoma after retrieving the needle, which was confirmed as microvascular damage inside the SMG during the subsequent surgical biopsy.

SMG surgical biopsy

All 18 patients underwent a surgical biopsy after SMG-CNB. During biopsy, the path of the CNB was identified in 16 of the 18 cases; in these case, the biopsies were obtained adjacent to the needle path. For the other two cases, tissues were sampled from the most suspicious lesions. The tissue volume from the SMG surgical biopsy ranged from 140 mm^3 to 455 mm^3 with a mean of 282.6 ± 91.3 mm^3. All SMG surgical biopsy samples underwent histopathological and immunopathological evaluation and were independently diagnosed as IgG4-RS by two pathologists.

All 18 samples presented typical histopathological characteristics, as shown in Fig. 2D–F. The periductal collagen sheath was observed in all 18 samples (100%), and obliterative phlebitis was observed in 16 out of 18 samples (88.9%). According to the histopathological classification, no sample was

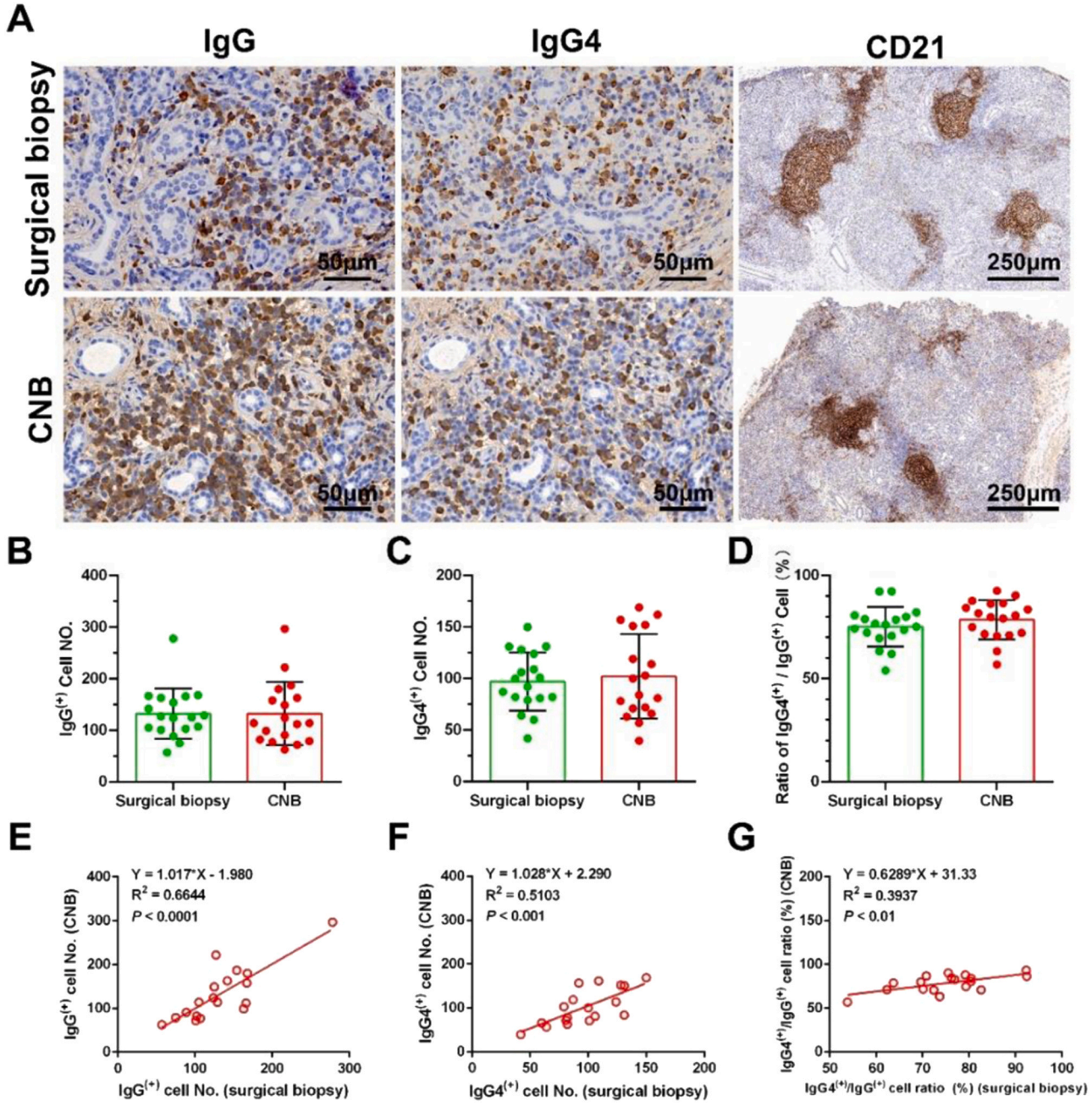

Fig. 3. Immunohistochemistry and staining analysis of SMG samples from IgG4-RS patients. (A) Representative images showing infiltration of a large number of IgG-positive and IgG4-positive plasma cells, as well as lymphoid follicle formation evidenced by CD21-positive follicular dendritic cells, in samples from both SMG-CNB and SMG surgical biopsy. There was no statistically significant difference in the number of IgG-positive plasma cells (B), number of IgG4-positive plasma cells (C), or IgG4-positive/IgG-positive plasma cell count ratio (D) between the SMG-CNB and SMG surgical biopsy samples. Pearson correlation analysis showed a strong significant correlation between SMG-CNB and SMG surgical biopsy samples for IgG-positive plasma cell count (E) and IgG4-positive plasma cell count (F), and a moderate significant correlation between SMG-CNB and SMG surgical biopsy samples for the ratio of IgG4-positive/IgG-positive plasma cells (G). Data are shown as the mean ± standard deviation values, $N = 18$. SMG, submandibular gland; CNB, core needle biopsy.

identified as stage 1, eight were classified as stage 2, and 10 as stage 3.

Massive infiltration of IgG-positive and IgG4-positive lymphoplasmacytic cells was observed in all samples (Fig. 3A). The average number of IgG-positive plasma cells was 132.2 ± 47.5 per high-power field, the average number of IgG4-positive plasma cells was 97.2 ± 27.6 per high-power field, and the average ratio of IgG4-positive/IgG-positive plasma cells was 75.2% ± 0.1% (Supplementary Material Table S1). Numerous CD21 stained lymphoid follicles were observed.

The procedure of SMG surgical biopsy was well tolerated, with no long-term complications. No injury of the marginal mandibular branch of the facial nerve occurred as a result of the surgery. The distal end of the facial artery and facial vein were ligatured in four of the 18 patients. Submandibular region swelling was observed as a transient complication in 12 cases, lasting approximately 1 week.

SMG core needle biopsy versus SMG surgical biopsy

Although the amount of tissue sampled by SMG-CNB was significantly lower than the SMG surgical biopsy ($P < 0.0001$), it was sufficient for histopathological evaluation and immunohistochemistry. Based on the SMG-CNB samples, all 18 cases were histopathologically and immunopathologically diagnosed as IgG4-RS, which was consistent with the SMG surgical biopsy samples. The diagnostic consistency of SMG-CNB and SMG surgical biopsy was 100%.

The tissue sampled by SMG-CNB presented similar histopathological characteristics to the SMG surgical biopsy samples; yet, there was still some slight difference. Obliterative phlebitis was a less frequent finding in SMG-CNB samples (83.3%) than in surgical biopsy samples (88.9%). In addition, in one patient, the histopathological evaluation of the sample suggested stage 1 for SMG-CNB and stage 2 for SMG surgical biopsy.

Regarding immunohistochemistry, there was no statistically significant difference in the number of IgG-positive plasma cells ($P = 0.99$), number of IgG4-positive plasma cells ($P = 0.67$), or IgG4-positive/IgG-positive plasma cell count ratio ($P = 0.29$) between tissues from CNB and surgical biopsy (Fig. 3B–D). Furthermore, Pearson correlation analysis showed a strong significant correlation between SMG-CNB samples and SMG surgical biopsy samples for the IgG-positive cell count ($P < 0.0001$) and IgG4-positive cell count ($P < 0.001$), and a moderate significant correlation for the ratio of IgG4-positive/IgG-positive cells ($P < 0.01$) (Fig. 3E–G).

Discussion

The histopathological and immunopathological characteristics are regarded as critical features for the diagnosis of IgG4-RS. The SMG is one of the most frequently involved organs of IgG4-RS and is also the most commonly selected site when proceeding with a biopsy because of its superficial location.[2,18] In SMG surgical biopsy, direct observation of the shape, texture, and glandular structures helps the physician collect representative samples and contributes to the accuracy of pathological diagnosis, making SMG surgical biopsy a reliable technique in diagnosing IgG4-RS. However, the surgical procedure inevitably leaves a scar and carries the risk of injury to the marginal mandibular branch of the facial nerve.

While attempts have been made to replace SMG surgical biopsy with minimally invasive means such as LSG biopsy,[8,19] researchers have found that pathological changes in the LSG are less evident and that LSG biopsy is insufficient for the diagnosis of IgG4-RS because of its low sensitivity. No alternative technique has hitherto been verified. CNB is still considered to have the greatest potential as a scarless method for IgG4-RS diagnosis; yet, no systematic research has been reported. In this study, SMG surgical biopsy was set as the gold standard diagnostic method, and a statistical evaluation of the diagnostic capability of SMG-CNB with some technical improvements for IgG4-RS diagnosis was evaluated.

It was hypothesized that the collection of a representative sample from typical pathological lesions during biopsy is the key point for an accurate diagnosis. In previous studies performed by the present authors,[2,17] it was revealed that the severity of fibrosis and inflammatory infiltration varies in a single gland, and that the superficial lobule of the SMG usually presents the most representative pathological characteristics. However, overlooking this pathological heterogeneity could be a critical cause of the inferior diagnostic capability of SMG-CNB that has been reported previously.[6]

Given this special characteristic, some technical improvements were made to the SMG-CNB procedure. The needle trajectory was designed to perform a parallel puncture into the superficial lobule of the SMG rather than a vertical puncture into the gland, so that the sampled core tissues were all from the superficial part of the SMG where pathological changes are usually more representative. The three-dimensional navigation system was used to guide the needle direction in real time. Moreover, the needle gauge size was increased to 14-gauge and the sampling depth of the biopsy instrument was set to 22 mm to obtain as much tissue as possible in a one-time puncture.

This study confirmed that the amount of tissue obtained from CNB was sufficient to proceed with the histopathological and immunopathological evaluations. More importantly, samples from SMG-CNB presented typical histopathological features, such as a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Immunopathological findings from SMG-CNB samples, including the IgG-positive plasma cell count, IgG4-positive plasma cell count, and ratio of IgG4-positive/IgG-positive plasma cells, were also in good concordance with the SMG surgical biopsy samples, as evidenced by the moderate or strong significant correlations. All 18 cases were independently diagnosed as IgG4-RS based on SMG-CNB samples, which was consistent with the SMG surgical biopsy diagnoses.

Despite the good consistency, there were still a few differences in histopathology between the SMG-CNB and SMG surgical biopsy samples. In one patient, the histopathological data suggested stage 1 after SMG-CNB and stage 2 after SMG surgical biopsy. This might have been due to the failure to identify the previous CNB path during the SMG surgical biopsy, and therefore sampling tissue from another suspicious section. Besides, due to the distinct difference in amount of tissue obtained, obliterative phlebitis was less likely to be found in CNB samples (83.3% in CNB samples, 89.9% in surgical biopsy samples in this study).

In terms of complications, a puncture parallel to the superficial part of the SMG avoids a penetrating injury and the possibility of a deeply located haematoma of the floor of the mouth, but raises the risk of injury to the facial artery and facial vein. Ultrasound can provide well-defined images of the vasculature in two-dimensional sagittal section views of the SMG, allowing the surgeon to keep the needle away from blood vessels thereby preventing injury. However, the superficial parts of the SMG usually show more representative pathological changes due to the pathological heterogeneity of IgG4-RS, hence a parallel puncture rather than a vertical puncture into the superficial lobules of the SMG is the preferred approach in the authors' opinion.

Three-dimensional guidance is needed to correct the needle direction. Therefore, in this study, CNB was preplanned and guided in real time by the navigation system. No injury to the facial artery or facial vein was observed during the CNB procedure among the 18 patients enrolled in this study; the only complication was microvascular damage inside the gland, which occurred in only one case.

This study has a few limitations. First, this was a single-centre study with a small sample size. Second, there was a limitation in the application of the navigation system in SMG-CNB, with an inevitable mismatch between the actual SMG location and the registered images, resulting from the change in head and neck position. This soft tissue shifting with the navigation system resulted in the failure to obtain tissue with the first puncture in one case. The deviation of the navigation system might be quantified by an intraoperative CT scan; however this would increase the patient's radiation exposure. Third, this study focused only on IgG4-RD according to the specific inclusion and exclusion criteria and disregarded other diseases presenting with a painless swelling in the head and neck region, such as malignant lymphoma and salivary gland tumours. Whether CNB could aid in the differential diagnosis of these malignant tumours remains to be studied.

In conclusion, tissues obtained from SMG-CNB were found to be sufficient for the histopathological diagnosis of IgG4-RS. The histopathological features and immunopathological findings based on SMG-CNB samples were in good concordance with SMG surgical biopsy. Sampling tissues from the superficial part of the SMG, where pathological changes are usually more representative, is the key point in SMG-CNB. On the basis of the study findings, standardized SMG-CNB is expected to replace SMG surgical biopsy for the diagnosis of IgG4-RS.

Ethical approval

This study was approved by the Ethics Committee for Human Experiments of Peking University School of Stomatology (Protocol Approval PKUSSIRB-202059178).

Funding

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Patient consent

All patients enrolled in this study provided written informed consent prior to participation.

Competing interests

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijom.2023.01.007.

References

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;**366**:539–51. https://doi.org/10.1056/NEJMra1104650
2. Li W, Chen Y, Sun ZP, Cai ZG, Li TT, Zhang L, Huang MX, Hua H, Li M, Hong X, Su JZ, Zhang ZY, Liu YY, He J, Li ZG, Gao Y, Yu GY. Clinicopathological characteristics of immunoglobulin G4-related sialadenitis. *Arthritis Res Ther* 2015;**17**:186. https://doi.org/10.1186/s13075-015-0698-y
3. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;**22**:21–30. https://doi.org/10.1007/s10165-011-0571-z
4. Wallace ZS, Naden RP, Chari S, Choi HK, Della-Torre E, Dicaire JF, Hart PA, Inoue D, Kawano M, Khosroshahi A, Lanzillotta M, Okazaki K, Perugino CA, Sharma A, Saeki T, Schleinitz N, Takahashi N, Umehara H, Zen Y, Stone JH. Members of the ACR/EULAR IgG4-RD Classification Criteria Working Group. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Ann Rheum Dis* 2020;**79**:77–87. https://doi.org/10.1136/annrheumdis-2019-216561
5. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Lohr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH. Second International Symposium on IgG4-Related Disease. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;**67**:1688–99. https://doi.org/10.1002/art.39132
6. Liu Y, Yang F, Chi X, Zhang Y, Fu J, Bian W, Shen D, Li Z. Needle biopsy compared with surgical biopsy: pitfalls of small biopsy in histological diagnosis of IgG4-related disease. *Arthritis Res Ther* 2021;**23**:54https://doi.org/10.1186/s13075-021-02432-y
7. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH. European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European consensus group. *Ann Rheum Dis* 2002;**61**:554–8. https://doi.org/10.1136/ard.61.6.554
8. Zhang YY, Hong X, Wang Z, Li W, Su JZ, Chen Y, Gao Y, Yu GY. Diagnostic utility of submandibular and labial salivary gland biopsy in IgG4-related sialadenitis. *Clin Rheumatol* 2020;**39**:3715–21. https://doi.org/10.1007/s10067-020-05097-1
9. Akiyama M, Kaneko Y, Hayashi Y, Takeuchi T. IgG4-related disease involving vital organs diagnosed with lip biopsy: a case report and literature review. *Medicine* 2016;**95**:e3970https://doi.org/10.1097/MD.0000000000003970
10. Ogawa Y, Nakagawa M, Ishii W, Ikeda S. Lip biopsy in Mikulicz's disease phenotype IgG4-related disease. *Intern Med* 2013;**52**:1007–8. https://doi.org/10.2169/internalmedicine.52.9443
11. Takano K, Keira Y, Seki N, Abe A, Yamamoto M, Takahashi H, Himi T. Evaluation of submandibular versus labial salivary gland fibrosis in IgG4-related disease. *Mod Rheumatol* 2014;**24**:1023–5. https://doi.org/10.3109/14397595.2013.853336

12. Moriyama M, Furukawa S, Kawano S, Goto Y, Kiyoshima T, Tanaka A, Maehara T, Hayashida JN, Ohta M, Nakamura S. The diagnostic utility of biopsies from the submandibular and labial salivary glands in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Int J Oral Maxillofac Surg* 2014;**43**:1276–81. https://doi.org/10.1016/j.ijom.2014.06.014
13. Takano K, Nomura K, Abe A, Kamekura R, Yamamoto M, Ichimiya S, Takahashi H, Himi T. Clinicopathological analysis of salivary gland tissue from patients with IgG4-related disease. *Acta Otolaryngol* 2016;**136**:717–21. https://doi.org/10.3109/00016489.2016.1154605
14. Detlefsen S, Mortensen MB, Pless TK, Cribe AS, de Muckadell OB. Laparoscopic and percutaneous core needle biopsy plays a central role for the diagnosis of autoimmune pancreatitis in a single-center study from Denmark. *Pancreas* 2015;**44**:845–58. https://doi.org/10.1097/MPA.0000000000000312
15. Ogiya A, Tanaka K, Tadokoro Y, Kikutani M, Uematsu T, Kashiwagi H, Kasami M, Takahashi K. IgG4-related sclerosing disease of the breast successfully treated by steroid therapy. *Breast Cancer* 2014;**21**:231–5. https://doi.org/10.1007/s12282-010-0225-6
16. Hirano K, Fukushima N, Tada M, Isayama H, Mizuno S, Yamamoto K, Yashima Y, Yagioka H, Sasaki T, Kogure H, Nakai Y, Sasahira N, Tsujino T, Kawabe T, Fukayama M, Omata M. Diagnostic utility of biopsy specimens for autoimmune pancreatitis. *J Gastroenterol* 2009;**44**:765–73. https://doi.org/10.1007/s00535-009-0052-8
17. Li W, Xie XY, Su JZ, Hong X, Chen Y, Gao Y, Zhang ZY, Yu GY. Ultrasonographic features of immunoglobulin G4-related sialadenitis. *Ultrasound Med Biol* 2016;**42**:167–75. https://doi.org/10.1016/j.ultrasmedbio.2015.09.014
18. Lin W, Lu S, Chen H, Wu Q, Fei Y, Li M, Zhang X, Tian X, Zheng W, Leng X, Xu D, Wang Q, Shen M, Wang L, Li J, Wu D, Zhao L, Wu C, Yang Y, Peng L, Zhou J, Wang Y, Sha Y, Huang X, Jiao Y, Zeng X, Shi Q, Li P, Zhang S, Hu C, Deng C, Li Y, Zhang S, Liu J, Su J, Hou Y, Jiang Y, You X, Zhang H, Yan L, Zhang W, Zhao Y, Zeng X, Zhang F, Lipsky PE. Clinical characteristics of immunoglobulin G4-related disease: a prospective study of 118 Chinese patients. *Rheumatology* 2015;**54**:1982–90. https://doi.org/10.1093/rheumatology/kev203
19. Moriyama M, Ohta M, Furukawa S, Mikami Y, Tanaka A, Maehara T, Yamauchi M, Ishiguro N, Hayashida JN, Kawano S, Ohyama Y, Kiyoshima T, Nakamura S. The diagnostic utility of labial salivary gland biopsy in IgG4-related disease. *Mod Rheumatol* 2016;**26**:725–9. https://doi.org/10.3109/14397595.2016.1148225

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