The determination of specificity, sensitivity and accuracy of core needle biopsy in the diagnosis of parotid and submandibular salivary glands tumors

Određivanje specifičnosti, senzitivnosti i tačnosti biopsije šupljom iglom u dijagnostikovanju tumora doušne i podvilične pljuvačne žlezde

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Abstract

Background/Aim. The diagnosis of tumors of salivary glands relies heavily on radiological examination and biopsy of pathological tissue. The aim of this study was to investigate the sensitivity, specificity and accuracy of core needle biopsy in diagnosis of tumors of parotid and submandibular glands. **Methods.** This study was designed as a cross-sectional clinical trial performed between May 2008 and May 2015 at the Department of Otorhinolaryngology and Maxillofacial Surgery, Clinical Center Zemun, Belgrade, Serbia. The examinations included 200 patients among which 100 were diagnosed with tumors of parotid salivary glands and 100 with tumors of submandibular salivary glands. The core needle biopsy was undertaken in all cases where tumor was smaller than 2 cm, far from blood vessels and far from the deep layer of parotid gland. The histopathological analysis was performed to identify histological type of the lesion. Upon performing the surgical procedure and consequently the tumor tissue extirpation, tissue samples obtained were investigated for the definitive diagnosis. **Results.** The sensitivity of the procedure was 90.9% for parotid salivary gland and 74% for submandibular salivary gland, the specificity was 95.9% for parotid salivary gland and 93% for submandibular salivary gland and the accuracy was 94.7% for parotid salivary gland and 87% for submandibular salivary gland. Based on the histopathological findings of the salivary glands obtained using core needle biopsy of the tumor tissue, it was possible to differentiate between malignant and benign lesions. **Conclusion.** Current investigation points to the advantages and efficiency of core needle biopsy in diagnosis of tumors of parotid and submandibular salivary glands.

Key words:
biopsy, fine-needle; biopsy, needle; diagnosis; histological techniques; parotid neoplasms; sensitivity and specificity; submandibular gland neoplasms.

Apstrakt

Uvod/Cilj. Dijagnoza tumora pljuvačnih žlezda se pretežno zasniva na radiološkom ispitivanju i histološkoj analizi patološke mase dobijene biopsijom. Cilj rada bio je da se ispitaju specifičnost, senzitivnost i tačnost biopsije šupljom iglom u dijagnozi bolesnika sa oboljenjima parotidne i submandibularne pljuvačne žlezde. **Metode.** Istraživanje je sprovedeno kao studija preseka u Odeljenju za otorinolaringologiju i maksilofacijalnu hirurgiju Kliničkog centra Zemun, Beograd, u periodu od maja 2008. do maja 2016. godine Studijom je bilo obuhvaćeno 200 bolesnika od kojih je kod 100 bio dijagnostikovan tumor u doušnoj pljuvačnoj žlezdi a kod 100 tumor u podviličnoj pljuvačnoj žlezdi. Biopsija šupljom iglom je bila sprovedena kod svih bolesnika kod kojih je tumor bio manji od 2 centimetara, udaljen od krvnih sudova i udaljen od dubokog režnja doušne pljuvačne žlezde. Posle toga je histološkim nalazom utvrđivan tip promene. Posle sprovođenja hirurške intervencije i potpunog uklanjanja obolelog tkiva, uzorak je ispitan za uspostavljanje konačne dijagnoze. **Rezultati.** Senzitivnost postupka iznosila je 90,9% za doušnu pljuvačnu žlezdu i 74% za podviličnu pljuvačnu žlezdu; specifičnost je bila 95,9% za doušnu pljuvačnu žlezdu; 93% za podviličnu pljuvačnu žlezdu i preciznost je bila 94,7% za doušnu pljuvačnu žlezdu i 87% za podviličnu pljuvačnu žlezdu. Na osnovu histopatološkog

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nalaza biopsije šupljom iglom bilo je moguće diferencirati maligne od benignih lezija. **Zaključak.** Sprovedeno istraživanje ukazuje na prednost i efikasnost biopsije šupljom iglom u dijagnozi tumefakata doušne i podvilične pljuvačne žlezde.

Ključne reči:
biopsija tankom iglom; biopsija iglom; dijagnoza; histološke tehnike; parotidne žlezde, neoplazme; senzitivnost i specifičnost; submandibularne žlezde, neoplazme.

Introduction

The pathology of parotid and submandibular salivary glands tumors includes variety of inflammatory lesions as well as benign and malignant tumors [1–3]. Notably, the treatment is heavily dependent on the results of the histopathological outcome [4]. Numerous studies have shown that 70% of parotid tumors belongs to neoplastic lesions and among those 75%–80% are benign which consequently demand to exclude nonneoplastic lesions to avoid unnecessary interventions [5]. Precisely, it is required to set a correct diagnosis and exclude congenital, granulomatous and inflammatory ethiological factors leading to the gland enlargement [6]. The proper diagnosis relies heavily on the clinical examination, radiological procedures using ultrasound or magnetic resonance imaging and laboratory findings, but for the definitive diagnosis, biopsy followed by the histopathological analysis is necessitated [7, 8]. It allows the discrimination between the neoplastic lesions that require surgical intervention and nonneoplastic lesions that may be treated conservative [8].

Among currently available noninvasive biopsy techniques, a fine needle aspiration cytology (FNAC) is the most commonly used for the diagnosis of tumors of salivary glands [9]. Based on the extensive work already reported on FNAC, the average sensitivity and specificity for FNAC are 80% and 90%, respectively. Novel literature findings report the sensitivity of FNAC between 64% and 90% and specificity between 86% and 100% [10, 11]. One of the drawbacks of this technique is its low sensitivity that comes as a consequence of difficulties in diagnosis of low differentiated carcinomas only by cellular morphology. Other downsides of this methodology are the high level of false negative findings and unreliable accuracy for different malignity differentiation. Yet, this technique is often followed by the cytology-fluorimetry, immunochistochemistry or extirpation biopsy for the definitive diagnosis. In addition, the preciseness of FNAC is dependent on the institution where the procedure is performed, experience of the operator, ultrasound guiding, the presence of cytologist in the institution and accessibility of the methods such as flow cytometry which is sometimes required for additional analysis. Therefore, relatively high sensitivity and specificity are true only for institution with the standardized procedures for FNAC [11–13].

Recent developments in pathology of salivary glands introduced a core needle biopsy (CNB) as diagnostic tool with its increased specificity and sensitivity and decreased number of false negative results in comparison to other biopsy techniques [14]. The advantages of CNB in comparison to FNAC include the possibility for routine histopathological analysis, differentiating between *in situ* and invasive lesions and excluding the possibilities for false benign lesion diagnosis. The additional advantages come as a consequence of avoiding the general anesthetics use, shorter time required for hospitalization and faster return of patients to usual activities [15, 16].

The investigators found an abundance of promising evidence for the suitability of CNB in different tumor diagnosis. However, a careful literature overview does not seem to reveal a vast amount of data regarding its applications in tumors of parotid and especially submandibular region of head and neck. Having in mind all unknown aspects of CNB in tumors diagnosis in the orofacial region the specific aim of this study was to determine the specificity, sensitivity and accuracy of CNB for the diagnosis of the parotid and submandibular region pathology.

Methods

Patients

The current study was performed as a cross-sectional clinical trial between May 2008 and May 2015 at the Department for Otorinolaringology and Maxillofacial Surgery of the Clinical Centre Zemun and included 200 patients. In 100 patients, the biopsies were performed in the parotid salivary gland and in 100 cases in submandibular salivary gland. In all patients, the clinical examination or ultrasound diagnosis confirmed the presence of tumors in parotid or submandibular salivary glands. The criteria for involvement in the study were as follows: age between 18 and 80 years and clinically and radiologically verified enlargement of parotid and submandibular salivary glands. All patients gave the informed consent for participation in the examinations. The criteria for the exclusion from the study were the patients who did not came back for the control examination. The investigation was performed after obtaining the Institutional Ethics Committee Approval from the Clinical Centre Zemun – Belgrade.

Computed tomography imaging

The parotid and sumbandibular salivary glands lesions in the investigated patients were imaged by using computed tomography imaging (CT) (MSCT, Toshiba) with the axial cross sections thickness measuring 0.5×0.3 mm and the width of the reconstructive interval of 0.2 mm. The CT scanning was performed in the native, arterial and venous phasis. Contrast was administered intravenously (70 mL) and the imaging was acquired after 65 s in order to obtain an optimum visualization of blood vessels of the neck.

Core needle biopsy

The CNB was performed by the same operator using the 18 gauge easy core biopsy device. The CNB was done after administration of local anesthetics (Xylocaine 1%) given under the skin by an insulin needle and minimally tissue damage. The knife No. 11 was used for incision and placements of needle pistol. After the needle administration, the tissue specimen was inserted into canila. The procedure was repeated twice. The specimens were stored in formalin solution and sent for the histopathological verification. In all cases where the intervention was performed, the extirpation biopsy was undertaken and sent to definitive histopathological diagnosis.

Histopathological analysis

The received specimens from the CNB were immersed overnight in 37% formalin solution for fixation, and processed with the standard methods for the histopathological analysis. All of the slides were stained with hematoxylin eosin (HE) method. In cases of diffuse large cell B lymphoma, or small cell lymphocytic lymphoma (diagnosis was established later on immunochistochemistry) only a slide description was made. The diagnosis of squamocellular carcinoma was readily made by using the slides from core biopsies.

Statistical analysis

The normality of the data distribution was evaluated by using the Kolmogorov-Smirnov test. The corresponding results were tabulated as true positive, true negative, false positive and false negative. Subsequently, the sensitivity, specificity and accuracy of CNB were calculated. The differences in the accuracy, specificity and sensitivity between the parotid and submandibular groups were compared by the χ^2 test. Tumor subtyping was performed in order to demonstrate the distribution of histopatological findings and to identify the most common histologically known cases with the false positive or false negative outcomes. A *p*-value less than 0.05 was considered a statistically significant.

Results

A total of 200 specimens from the parotid and submandibular gland were examined, among which 100 were from the parotid gland and 100 from the submandibular gland. Initially, in a preoperative phase, the salivary gland tissue was obtained by using the CNB, and the histopathological examination was performed. Thereafter, the final histopathological diagnosis was established by the examination of the salivary gland tissue obtained by the extirpation biopsies during the definitive surgical procedure. The patients with parotid tumors were divided into the groups of benign lesions (n = 73), or malignant (n = 22) conditions based on the final diagnosis. In the submandibular group, the same was undertaken for the benign (n = 61) and malignant (n = 31) cases. Five inadequate specimens in the parotid and 8 in the submandibular group were found. The accuracy, specificity

and sensitivity of CBN are shown in table 1. There was no statistical significant difference in specificity finding between the parotid and the submandibular group, while the significantly higher sensitivity and accuracy were found in the parotid group (*p* < 0.05) (Table 1). The unsatisfactory tumor diagnosis tended to be higher in the submandibular salivary glands group (Table 2).

Table 1

Comparison of diagnostic accuracy values of core needle biopsy in tumors of parotid and submandibular salivary glands

Characteristic	Specimens	
	parotid (n = 100)	submandibular (n = 100)
Specimens (n)		
adequate	95	92
inadequate	5	8
false negative malignant	2	8
true positive malignant	20	23
true negative benign	70	57
false positive benign	3	4
Sensitivity (%)	90.9	74 *
Specificity (%)	95.9	93
Accuracy (%)	94.7	87 *

Statistically significant in comparison to the results obtained for parotid gland.

The CT images of tumors in the parotid and submandibular region are shown in Figure 1. Figures 2 and 3 reveal the histopathological findings in some of the investigated cases.

Discussion

The presence of tumors in parotid or submandibular salivary glands is a huge diagnostic and therapeutic challenge. Nonneoplastic, benign neoplasms or malignancies may cause such tumors [1, 17]. To this purpose, the CNB was used in the current investigation to obtain the representative specimens of tumor tissue and evaluate the possibility to differentiate the tumor subtypes after the histopathological analysis. The obtained results consistently indicated that the CNB are nearing the point when it can be considered as the option of the first resort in the salivary gland diagnosis. Methodology used may be considered representative and highly complementary with procedures widely accepted in clinics.

In the opinion of Kraft et al. [10], the evaluation of novel diagnostic techniques like the CNB should be performed by comparing the results obtained after the CNB and histolological findings after the extirpation biopsy. This methodological approach was followed in the current investigation. In line with the results of this study, the relevant literature data confirm the suitability of CNB for the salivary glands tumors diagnosis.

Table 2
Unsatisfactory rates of core needle biopsy (CNB) in the salivary glands tumors according to the histological diagnosis

Neoplasms by histologic type	Unsatisfactory rates of CNB	
	parotid salivary gland	submandibular salivary gland
Malignant		
Carcinoma of salivary gland		
adenocarcinoma	0/2	1/5
carcinoma of acinus cells	1/2	0/4
cystadenocarcinoma	0/1	0/1
mucoepidermoid carcinoma	0/1	2/2
Lymphoma		
Hodgkin	0/5	1/4
non Hodgkin	0/3	1/4
Metastasis in lymph nodes		
squamous cell carcinoma	1/5	1/6
adenocarcinoma of prostate	0/1	1/1
melanoma	0/2	1/3
undifferential carcinoma of nasothroath (UCNT)	0/0	0/1
Subtotal	2/22	8/31
Benign		
Adenoma		
pleomorphic adenoma	3/53	3/33
adenoma of basal cells	0/2	0/5
oncocytoma	0/2	0/5
lymphadenoma	0/4	1/16
basal cells adenoma	0/7	0/1
lypoms	0/5	0/1
Subtotal	3/73	4/61
Total	5/95	12/92
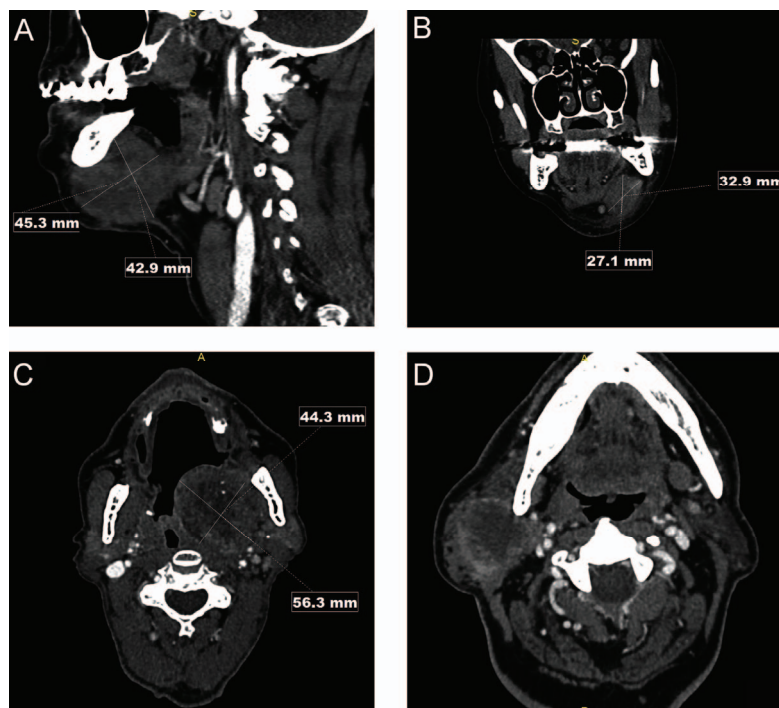
Fig. 1 – Computed tomography imaging of tumors lesions in: A, B) submandibular and C, D) parotid salivary gland. A) Coronal cross section of tumor lesion in the left submandibular salivary gland is characterized as a soft tissue lesion measuring 45.3 mm × 42.9 mm; B) The sagittal cross section of tumor lesion in the left submandibular salivary gland measuring 32.9 mm × 27.1 mm; C) The saggital cross section of tumor lession in the right parotid salivary gland measuring 44.3 mm × 56.3 mm with invasion into the deep lobe of salivary gland; D) The tumor lession in the superficial part of the left parotid salivary gland (hematoxylin eosin staining, 200×).
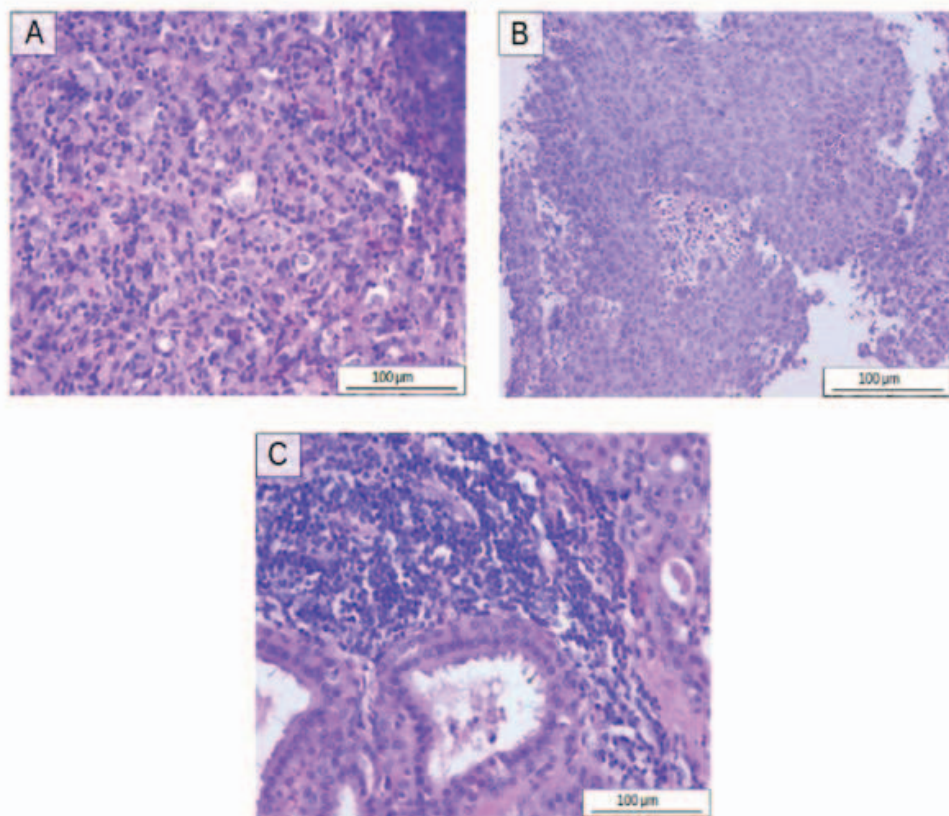
Fig. 2 – Histology of tumors in the parotid salivary gland: A) A classic Hodgkin lymphoma can be recognized in the hematoxylin eosin core biopsy samples without difficulty by the presence of Reed Sternberg cell and its variants, even though their number can vary from case to case. In the most common type of Hodgkin disease, nodular sclerosis Hodgkin disease, numerous lacunar cells can be identified as large cells with polylobular nuclei and small nucleoli. Their acidophilic cytoplasm is affected by formalin fixation, so that the cells seem to lodge in an artificial lacuna. When such cells are seen in an admixture of inflammatory cells (lymphocytes, eosinophils), the diagnosis is usually straightforward, along with the adequate phenotype findings; B) Squamous cells carcinoma, especially when well differentiated, can be recognized as an epithelial neoplasm of large to medium cells with the ample eosinophilic cytoplasm, distinct cellular borders and large vesicular nuclei with the prominent nucleoli. Foci of keratinization can also be identified, as well as the mitotic figures; C) Warthin tumor, as a benign neoplasm, is a biphasic tumor, composed of a heavy lymphocytic infiltrate and an epithelial component of oncocytes. The glandular structures of this tumor are lined by two rows of large cells with intensive eosinophilic cytoplasm with basally oriented regular nuclei (hematoxylin eosin staining, 100×).
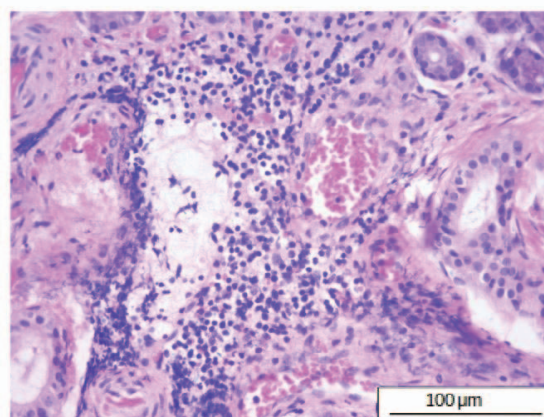
Fig. 3 – Histology of tumor in the submandibular salivary gland. Tissue of mixed salivary glands is observed showing the signs of chronic sclerosing inflammation as well as dilatation of largerducts. Foci of microhemorrage are also noted (hematoxylin eosin staining, 200×).

Howlett et al. [15] demonstrated the CNB sensitivity and specificity of 100% in the histopathological verification of neoplasms by evaluating 135 patients with tumors in the parotid region. In another study on the same topic, Screaton et al. [18] showed the sensitivity of 98%, specificity of 100% and preciseness of 99% of CNB in differentiating between the benign and malignant lympadenopathy. However, it is to note that only 23% of the patients were subjected to the open biopsy of lymphatic nodes of neck dissection while in the rest of the patients' diagnosis was confirmed by the clinical and laboratory findings. Also, in accordance to a meta-analysis performed by Schmidt et al. [11], the average sensitivity and specificity of CNB was 80% and 97% respectively. Recent investigations showed that the sensitivity and specificity of ultrasound guided CNB is even higher, 99%–100% [5, 19].

Although scientific literature provides information on the diagnosis of tumors of using the CNB, FNAC and extirpation biopsy, the limited data is available to compare those procedures on the same patient. The investigators who compared the FNAC and CNB on the same tissue found an accuracy of CNB and FNAC to be 83% and 64%, respectively [20]. Also, an investigation of FNAC or CNB combined with a subsequent incision biopsy of the same bioptic mass showed the accuracy of incision biopsy was 100%, the accuracy of FNAC was 75% and the accuracy of CNB was 80.7%. However, in that study the histopathological diagnosis could be established correctly in only 33% of cases after FNAC and in 45% cases after the CNB. Therefore, the authors suggested the incision biopsy as a definitive diagnostic tool [10].

The CNB presents a safe, simple and efficient diagnostic procedure with preciseness higher than 97% in the diagnosis of parotid tumors [21]. It provides improved possibilities for obtaining the specimen of higher volume in comparison with FNAC decreasing the level of nonrepresentativity (in FNAC incidence is 8.1% and in the CNB 1.2%). This is of paramount importance in smaller medical centers where pathologists are not capable to analyze specimens immediately. In addition, the CNB preserves the histological architecture increasing the preciseness of the diagnosis and enabling the additional diagnostic procedures such as an immunohistochemically analysis [22]. The advantages of CNB are documented especially in cytological diagnosis of pleomorphic adenoma, Wartin's tumor and lymphoma that are traditionally hard to diagnose using only FNAC [23, 24]. Using the needles of different size leads to the same results, although the 18 gauge is considered the most appropriate. Several drawbacks of CNB observed during current investigation are related to the necessity for local anesthesia during the biopsy procedure, since the procedure is painful and morbidity is higher in comparison to FNAC if not performed properly [25]. Majority of studies have shown that, in the patients with tumors such as fibrosarcoma, pleomorphic skeletal sarcoma and hondroma, there is a high possibility for their dissemination into salivary glands tissue [16, 26].

An important advantage of CNB is the possibility to allow for the precise identification of pathological structures during the histopathological examination, while in FNAC, a histologist is capable only of detecting cells morphology. It is also significant to note that the increased speed of needle administration in the CNB technique decreased the necessity to move the patient during the procedure and consequent noncomfort [14, 27]. The patients who were previously subjected to radiological treatment due to the tumors in the region of neck are especially not indicated for FNAC owing to the presence of scar tissue and hence the CNB is preferable in such cases [27, 28]. In addition, the CNB provides the superior diferentiation between limphoid hyperplasia from lymphoma than FNAC as well as improved identification of different types and carcinoma grading [10].

From the clinical point of view, the difficulties arise when trying to establish whether the salivary tumor originates from the tissue of salivary gland, or it presents the metastasis of the tumors of other organs. It should be born in mind that in the recent years, due to the general increase in tumors incidence, the possibility for the metastasis to occur in the tissue of the salivary gland is also increased. The current widely accepted clinical and diagnostic approaches in salivary gland diagnosis do not provide possibility to precisely point to the exact origin of the tumor without biopsy [29, 30]. The present study confirms the increase in the metastatic tumors in the tissue of salivary glands. In this investigation, it is documented that higher malignancies could be observed in the submandibular salivary gland than in the parotid one, and consequently, the higher amount of metastatic cases were also observed within the submandibular salivary gland. Thus, the possibility to diagnose the tumors of other organs when performing the CNB of salivary glands is higher in the case of submandibular salivary glands. The discrimination between the primary tumor of the gland and metastasis is also important for the treatment of the metastatic tumors because in such case the most important issue is to determine the primary tumor location. The CNB is of paramount importance for metastasis of primary tumors as a simple and reliable technique that can be performed in the outpatient conditions and have a significant influence in preventive diagnostic procedures, having the benefit for both diagnostics and the therapy of patients. For instance, it was easily observed in the current investigation in the case of undifferential carcinoma of nasothroat (UCNT) that it could be diagnosed with difficulty in this primary stadium without the established CNB of submandibular salivary gland. In addition, in elderly patients where chronic inflammatory conditions resemble to the great extent the tumors, the CNB was a very reliable procedure to discriminate between those two pathologies.

Regarding the anatomical difference in the lymphatic nodes position in parotid and submandibular salivary gland, it should be noted that the lymphatic nodes in the parotid salivary glands are located within the gland tissue and in the case of submandibular salivary gland lymphatic nodes circumvent the submandibular gland in a close contact with the gland tissue - this complex of salivary gland-lymphatic nodes is considered to be a unit where the CNB was performed. In other words, metastases found in the lymphatic nodes surrounding the submandibular gland were considered in the present research as the gland metastasis.

The current investigation has some limitations. First, there are limited data in the literature related to the use of CNB for diagnosis of tumors of submandibular salivary glands which limits the possibilities for studies comparison. Yet, the real volume of biopsy tissue required for each case was in few instances smaller than initially estimated. Finally, it is not safe to assume that there were not the cases with dissemination of tumor tissue after biopsy because the patients were not monitored after the procedure long enough for such a conclusion (usually 20 years is required). However, all necessary measures were performed to minimize such a scenario including the excision of the needle pathway after excision, chemotherapy in the case of lymphoma presence and avoiding multiply injection into tumor tissue. From the pathological point of view, the limitation of CNB includes the diagnosis of Hodgkin and non-Hodgkin lymphomas – it was not possible to discriminate between those two tumors using the CNB technique. Although the literature data claim that the CNB is a suitable technique for such cases, these observations are mainly based on the radiological approaches that, in the opinion of the investigators of the current study, could not be easily performed in the routine clinical practice.

Conclusion

The results obtained here for the tumors of parotid and submandibular region demonstrated the high sensitivity, specificity and accuracy of CNB as a diagnostic tool, and hence provide an additional verification for the suitability of the CNB in the clinical practice. Collectively, the data observed in the present study support the assumption that the CNB may be considered as a safe alternative to the open biopsy in the diagnosis of head and neck tumors. This technique is safe in all patients due to a short procedure and fewer complications in comparison to the excision biopsy. Altogether, the results of this study strongly recommend the use of CNB as a suitable and safe diagnostic tool in the pathology of parotid and submandibular salivary glands.

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R E F E R E N C E S

1. *Margeta J*. Sialolithiasis of the submandibular gland. Vojnosanit Pregl 1967; 24(4): 211–4. (Serbian)
2. *Cvetinović M, Stosić S, Jović N*. How we have treated parotid gland tumors. Vojnosanit Pregl 1997; 54(4 Suppl): 45–52.
3. *Yamashita Y, Kurokawa H, Takeda S, Fukuyama H, Takahashi T*. Preoperative histologic assessment of head and neck lesions using cutting needle biopsy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 93(5): 528–33.
4. *Kuan EC, Mallen-St Clair J, John MA*. Evaluation of Parotid Lesions. Otolaryngol Clin North Am 2016; 49(2): 313–25.
5. *Pfeiffer J, Kayser G, Technau-Ihling K, Boedeker CC, Ridder GJ*. Ultrasound-guided core-needle biopsy in the diagnosis of head and neck masses: Indications, technique, and results. Head Neck 2007; 29(11): 1033–40.
6. *Shives TC*. Biopsy of soft-tissue tumors. Clin Orthop Relat Res 1993; (289): 32–5.
7. *Curtin HD, Brogle N, Caruso P*. Imaging-Guided Biopsy. Atlas Oral Maxillofac Surg Clin North Am 2005; 13(1): 51–62.
8. *Haldar S, Sinnott JD, Tekeli KM, Turner SS, Howlett DC*. Biopsy of parotid masses: Review of current techniques. World J Radiol 2016; 8(5): 501.
9. *Huang Y, Wu C, Lin G, Chuang W, Yeow K, Wan Y*. Comparison of ultrasonographically guided fine-needle aspiration and core needle biopsy in the diagnosis of parotid masses. J Clin Ultrasound 2011; 40(4): 189–94.
10. *Kraft M, Laeng H, Schmuziger N, Arnoux A, Gürtler N*. Comparison of ultrasound-guided core-needle biopsy and fine-needle aspiration in the assessment of head and neck lesions. Head Neck 2008; 30(11): 1457–63.
11. *Schmidt RL, Jedrzkiewicz JD, Allred RJ, Matsuoka S, Witt BL*. Verification bias in diagnostic accuracy studies for fine- and core needle biopsy of salivary gland lesions in otolaryngology journals: A systematic review and analysis. Head Neck 2014; 36(11): 1654–61.
12. *Shetty A, Geethamani V*. Role of fine-needle aspiration cytology in the diagnosis of major salivary gland tumors: A study with histological and clinical correlation. J Oral Maxillofac Pathol 2016; 20(2): 224–9.
13. *Haldar S, Mandalia U, Skelton E, Chow V, Turner SS, Ramesar K, et al*. Diagnostic investigation of parotid neoplasms: a 16-year experience of freehand fine needle aspiration cytology and ultrasound-guided core needle biopsy. Int J Oral Maxillofac Surg 2015; 44(2): 151–7.
14. *Domanski HA, Akerman M, Carlén B, Engellau J, Gustafson P, Jonsson K, et al*. Core-needle biopsy performed by the cytopathologist: a technique to complement fine-needle aspiration of soft tissue and bone lesions. Cancer 2005; 105(4): 229–39.
15. *Howlett DC, Menezes LJ, Lewis K, Moody AB, Violaris N, Williams MD*. Sonographically Guided Core Biopsy of A Parotid Mass. AJR Am J Roentgenol 2007; 188(1): 223–7.
16. *Altuntas AO, Slavin J, Smith PJ, Schlict SM, Powell GJ, Ngan S, et al*. Accuracy Of Computed Tomography Guided Core Needle Biopsy Of Musculoskeletal Tumours. ANZ J Surg 2005; 75(4): 187–91.
17. *Jankovic-Velickovic L, Dimov I, Petrovic D, Stojnev S, Dacic S, Velickovic S, et al*. Stromal reaction and prognosis in acinic cell carcinoma of the salivary gland. Vojnosanit Pregl 2013; 70(12): 1155–8.
18. *Screaton NJ, Berman LH, Grant JW*. Head and Neck Lymphadenopathy: Evaluation with US-guided Cutting-Needle Biopsy. Radiology 2002; 224(1): 75–81.
19. *Song IH, Song JS, Sung CO, Roh J, Choi S, Nam SY, et al*. Accuracy of Core Needle Biopsy Versus Fine Needle Aspiration Cytology for Diagnosing Salivary Gland Tumors. J Pathol Transl Med 2015; 49(2): 136–43.
20. *Howlett DC, Skelton E, Moody AB*. Establishing an accurate diagnosis of a parotid lump: evaluation of the current biopsy methods – fine needle aspiration cytology, ultrasound-guided core biopsy, and intraoperative frozen section. Br J Oral Maxillofac Surg 2015; 53(7): 580–3.
21. *Cunningham JD, McCusker MW, Power S, PearlyTi J, Thornton J, Brennan P, et al*. Accessible or Inaccessible? Diagnostic Efficacy of CT-Guided Core Biopsies of Head and Neck Masses. Cardiovasc Intervent Radiol 2015; 38(2): 422–9.
22. *Trenkić-Božinović M, Katić V, Krasić D, Veselinović D, Jovanović P, Krstić M*. Clinical, histopathological and immunohistological

study of lymphoid disorders in the parotid gland of patients with Sjögren's syndrome. Vojnosanit Pregl 2009; 66(12): 955–60.

23. *Tatić V, Cvetinović M, Knezević M, Milenković D.* Association of pleomorphic adenoma and Warthin's tumor in the parotid gland. Case report. Vojnosanit Pregl 1990; 47(6): 446–8.

24. *Ridder GJ, Technau-Ihling K, Boedeker CC.* Ultrasound-Guided Cutting Needle Biopsy in the Diagnosis of Head and Neck Masses. Laryngoscope 2005; 115(2): 376–7.

25. *Yang TL, Chen CN.* Application of Ultrasound-guided Core Biopsy in Head and Neck. J Med Ultrasound 2014; 22(3): 133–9.

26. *Salapura-Dugonjić A, Knezević-Usaj S, Eri Z, Tadić-Latinović L.* Significance of microvessel density in prostate cancer core biopsy. Vojnosanit Pregl 2015; 72(4): 317–27.

27. *Arnold D, Goodwin W, Weed D, Civantos F.* Treatment of recurrent and advanced stage squamous cell carcinoma of the head and neck. Semin Radiat Oncol 2004; 14(2): 190–5.

28. *Kao J, Garofalo MC, Milano MT, Chmura SJ, Citron JR, Haraf DJ.* Reirradiation of recurrent and second primary head and neck malignancies: a comprehensive review. Cancer Treat Rev 2003; 29(1): 21–30.

29. *Grundmann T, Hohenberg H, Herbst H.* Tissue sampling in the deep head-neck area with a new ultrasound-controlled, semi-automatic micro-punch biopsy device. HNO 2000; 48(8): 583–8. (German)

30. *Kesse KW, Manjaly G, Violaris N, Howlett DC.* Ultrasound-guided biopsy in the evaluation of focal lesions and diffuse swelling of the parotid gland. Br J Oral Maxillofac Surg 2002; 40(5): 384–8.