



Diagnostic Value of Fine-Needle Aspiration Biopsy in Major Salivary Gland Masses

Majör Tükrük Bezi Kitlelerinde İnce İğne Aspirasyon Biyopsisinin Tanısal Değeri

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ABSTRACT

Objective: To investigate the diagnostic efficacy and accuracy of fine-needle aspiration biopsy (FNAB) in solid and cystic tumors of the major salivary glands, examine the histopathologic distribution and malignancy rates of non-diagnostic cases, and investigate any significant difference between benign and malignant salivary gland tumors according to age and tumor size

Methods: Age, sex, tumor location, side, tumor size, preoperative diagnosis of FNAB, and final histopathological diagnosis of 182 patients with major salivary gland mass were retrospectively evaluated. Each lesion is categorized as solid and cystic. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and FNAB accuracy were separately calculated for parotid gland tumors, submandibular gland tumors, solid, and cystic tumors.

Results: Among the 182 performed FNABs, 153 were benign, 9 were malignant, and 20 were non-diagnostic. Malignancy was detected in 12.2% of the parotid gland, 25.9% of the submandibular gland, and 14.2% overall. Unlike the parotid gland, when the FNAB of the submandibular gland was non-diagnostic, the final histopathology was most likely to be malignant than benign. No difference was found in the risk of malignancy between the solid and cystic tumors ($p=0.192$). The sensitivity, specificity, PPV, NPV, and accuracy of the major salivary gland FNAB in this study were 42.1%, 99.3%, 88.8%, 92.8%, and 92.5%, respectively.

Conclusion: In the context of a non-diagnostic FNAB, high suspicion especially for the submandibular gland tumors is warranted for otorhinolaryngologists. Based on low sensitivity values, FNAB of the major salivary glands is limited as the only diagnostic tool.

Keywords: Fine-needle aspiration biopsy, malignancy, salivary gland, sensitivity, specificity

ÖZ

Amaç: Majör tükrük bezlerinin solid ve kistik tümörlerinde ince iğne aspirasyon biyopsisinin (İİAB) tanısal etkinliğinin ve doğruluğunun araştırılması, non-diagnostik olguların histopatolojik dağılımının ve malignite oranlarının incelenmesi, yaş ve tümör boyutuna göre benign ve malign tükrük bezi tümörleri arasındaki farkın araştırılması amaçlanmıştır.

Gereç ve Yöntem: Majör tükrük bezi kitlesi olan 182 hastanın yaşı, cinsiyeti, kitle lokalizasyonu, tarafı, kitlenin boyutu, preoperatif İİAB tanısı ve son histopatolojik tanısı retrospektif olarak değerlendirildi. Her bir lezyon solid ve kistik olarak kategorize edildi. Parotis bezi tümörleri, submandibuler bez tümörleri, solid ve kistik tümörler için duyarlılık, özgüllük, pozitif predediktif değeri (PPV), negatif prediktif değeri (NPV) ve doğruluğu ayrı ayrı hesaplandı.

Bulgular: Gerçekleştirilen 182 İİAB'den 153'ü benign, 9'u malign ve 20'si non-diagnostik idi. Parotis bezi kitlelerinin %12,2'si, submandibuler bez kitlelerinin %25,9'u ve tüm majör tükrük bezi kitlelerinin ise %14,2'si maligndi. Parotis bezinden farklı olarak, submandibuler bezin İİAB'si non-diagnostik olduğunda, histopatolojik tanı büyük oranda (%80) maligndi. Solid ve kistik tümörler arasında malignite riski açısından fark yoktu ($p=0,192$). Bu çalışmada majör tükrük bezi İİAB'nin duyarlılığı, özgüllüğü, PPV, NPV ve doğruluğu sırasıyla %42,1, 99,3, 88,8, 92,8 ve %92,5 olarak bulundu.

Sonuç: Özellikle submandibuler bez tümörleri için non-diagnostik bir İİAB varlığı, yüksek malignite şüphesi açısından kulak burun boğaz uzmanları için uyarıcı olabilir. Majör tükrük bezi tümörlerinde İİAB'nin düşük duyarlılık değerleri nedeniyle tek başına bir tanı aracı olarak kullanımı sınırlıdır.

Anahtar Kelimeler: İnce iğne aspirasyon biyopsisi, malignite, tükrük bezi, duyarlılık, özgüllük

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INTRODUCTION

Major salivary gland tumors account for 3-10% of the head and neck cancers and represent a various and heterogeneous group of neoplasms with complex clinicopathologic characteristics and different biological behavior. Their diversity makes the diagnosis challenging (1,2). Treatment of choice for salivary gland tumors is based on clinical evaluation and diagnostic tests: ultrasonography, fine-needle aspiration biopsy (FNAB), endoscopic ultrasound-guided fine-needle aspiration, biopsy, computed tomography, and magnetic resonance imaging (3). FNAB is a safe and reliable tool for salivary gland lesion diagnosis. It is simple, relatively painless, and easily repeated if another sample is needed. However, its diagnostic accuracy is still controversial despite being used for many years (4).

Several non-neoplastic lesions, benign neoplasms, and malignancies of the salivary gland present with a predominant or minor cystic component (5). Distinguishing these lesions from one another is important since patient management often differs among these groups. FNAB is often used to guide management decisions; however, it is frequently non-diagnostic in assessing cysts, as the aspirate may only capture cystic fluid. Despite non-diagnostic FNAB results, at least one-third of cystic salivary gland lesions are neoplastic (6,7).

This study aimed to investigate the diagnostic efficacy and accuracy of FNAB in solid and cystic tumors of the major salivary glands, examine the histopathologic distribution and malignancy rates of non-diagnostic cases, and investigate any significant difference between benign and malignant salivary gland tumors according to age and tumor size.

METHODS

Between February 2010 and February 2020, 267 cases that undergone parotidectomy or submandibular gland resection due to major salivary gland tumors in the otorhinolaryngology department of our tertiary referral center were retrospectively examined. Patients who underwent open biopsy before surgery, patients with unavailable FNAB, patients with non-diagnostic cytology depend on insufficient cellularity, and patients with preoperative FNAB done at an outside hospital, except in the situation where the original slides were transferred to our center for review by our institution pathologists, were excluded. Age, sex, tumor location, side, tumor size as measured by ultrasound/computed tomography/magnetic resonance imaging (by measuring the largest diameter of tumor), preoperative FNAB diagnosis, and final histopathological diagnosis were

noted. Major salivary gland lesions were categorized as solid and cystic (pure cystic or has a cystic component in radiologic imaging studies) based on radiology reports and from available ultrasound, computed tomography, and/or magnetic resonance imaging studies. In addition, patients without any imaging studies or those with insufficient imaging report details were excluded. The study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (date: 17.02.2020, no: 2020/77). The study was conducted by the principles of the Helsinki declaration.

All of the FNAB was performed under ultrasound guidance using a 25 gauge needle and standard aspiration technique without local anesthesia in the radiology department of our hospital. The needle is inserted from a single point and moved in 3-4 directions through the tumor. After obtaining enough samples, the needle is withdrawn and detached from the syringe. The aspirate is sprayed on at least 4 glass slides, smeared, fixed in alcohol for hematoxylin-eosin stain, and sent to the pathology laboratory. All specimens were examined in the Pathology Department of our hospital. Preoperative cytological findings of the FNAB were classified as benign, non-diagnostic, and malignant. The subtypes were noted if possible. Final histopathological diagnosis was grouped as benign and malignant, and typing was noted. When the FNAB is non-diagnostic, our usual practice in such cases is to perform a second FNAB, if the cytological diagnosis is still not obtained with the second FNAB, then it is accepted as non-diagnostic.

FNAB results were compared to the final surgical pathology. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and FNAB diagnostic accuracy was calculated, and patients with non-diagnostic cytology were excluded from this analysis. Sensitivity, specificity, PPV, NPV, and FNAB accuracy were separately calculated for parotid gland tumors, submandibular gland tumors, solid, and cystic tumors, and also patients with non-diagnostic cytology were excluded from this analysis. The Mann-Whitney U test was used to examine the relationship of age and tumor size with the final histopathological diagnosis. The risk of malignancy between solid and cystic tumors was examined with the chi-square test. The confidence interval was 95% and p-values of <0.05 were considered to be significant.

RESULTS

Of the 267 retrospectively investigated patients, 85 were excluded due to unavailable FNAB results and/or insufficient

details of imaging reports. A total of 182 patients were retrospectively examined, wherein 95 (52.2%) were male and 87 (47.8 %) were female, with an average age of 49.07±16.43 years (range: 10-82 years). The mean age of patients with benign final histopathology was 48.79±15.96 years (range: 10-80 years, median: 52 years), whereas 50.77±19.23 years (range: 14-82 years, median: 56 years) in malignant tumors, without any statistically significant difference (p=0.7). The mean size of the salivary gland tumors with benign final histopathology was 27.41±14.37 mm (range: 5-65 mm, median: 25 mm), whereas 30.61±16.33 mm (range: 16-120 mm, median: 27 mm) in malignant ones. No statistically significant difference was found between the benign and malignant tumors (p=0.348).

Samples were obtained from the parotid in 155 (85.2%, 76 right parotids, 79 left parotids) cases and submandibular in 27 (14.8%, 13 right submandibular, 14 left submandibular) cases. Among the 182 performed FNABs, 153 (84%) were benign, 9 (4.9%) were malignant, and 20 (10.9%) were non-diagnostic. FNAB distribution and final histopathologic results among the parotid and submandibular gland tumors are shown in Table 1. Malignancy was detected in 12.2% (n=19) of the parotid gland tumors, 25.9% (n=7) of the submandibular gland tumors, and 14.2% (n=26) overall based on final histopathology. The most common benign diagnosis among the parotid gland tumors were pleomorphic adenoma (n=69, 50.7%) and Warthin's tumor (n=50, 36.7%), whereas the most common malignant diagnoses were mucoepidermoid carcinoma (n=5, 26.3%) and acinic cell carcinoma (n=4, 21%; Table 2). The most common benign diagnosis among the submandibular gland tumors was pleomorphic adenoma (n=19, 95%) and the most common malignant diagnosis was adenoid cystic

carcinoma (n=2, 28.5%; Table 3). When the FNAB of the parotid gland is non-diagnostic, the final histopathology was most likely to be benign (80%) than malignant (20%). In contrast, when the FNAB of the submandibular gland was non-diagnostic, the final histopathology was most likely to be malignant (80%) than benign (20%). The distribution of final histopathology in non-diagnostic FNAB cases was presented in Table 4. A total of 125 solid (68.6%) and 57 cystic tumors (31.3%) (19 pure cystic, 38 have cystic component) were found among the major salivary gland tumor cases. FNAB of solid tumors accounting for 14 (11.2 %) were non-diagnostic, whereas 6 (10.5%) FNAB of cystic tumors were non-diagnostic (Table 5). Malignancy was detected in 12% (n=15) of solid tumors and 19.2% (n=11) in cystic tumors based on final histopathology. A higher malignancy rate was

Table 1. Distribution of FNAB results and final histopathologic diagnosis among parotid and submandibular gland tumors

FNAB diagnosis	Final histopathologic diagnosis, n (%)	
	Benign	Malignant
Parotid gland		
Benign (n=132)	123 (93.1)	9 (6.8)
Malignant (n=8)	1 (12.5)	7 (87.5)
Non-diagnostic (n=15)	12 (80)	3 (20)
Submandibular gland		
Benign (n=21)	19 (90.4)	2 (9.5)
Malignant (n=1)	0 (0)	1 (100)
Non-diagnostic (n=5)	1 (20)	4 (80)

FNAB: Fine-needle aspiration biopsy

Table 2. Final histopathologic diagnosis of parotid gland lesions

	n	%
Benign (n=136)		
Pleomorphic adenoma	69	50.7
Warthin tumor	50	36.7
Granulomatous sialadenitis	2	1.4
Lymphoepithelial sialadenitis	2	1.4
Lymphoepithelial cyst	2	1.4
Lipoma	2	1.4
Oncocytoma	2	1.4
Basal cell adenoma	1	0.7
Castleman disease	1	0.7
Epidermoid cyst	1	0.7
Int alymphoid epidermoid cyst	1	0.7
Cavernous hemangioma	1	0.7
Non-specific chronic sialadenitis	1	0.7
Parotid duct cyst	1	0.7
Malignant (n=19)		
Mucoepidermoid carcinoma	5	26.3
Acinic cell carcinoma	4	21
Ductal carcinoma	2	10.5
Myoepithelial carcinoma	2	10.5
Squamous cell carcinoma	2	10.5
Adenoid cystic carcinoma	1	5.2
B-cell non-hodgkin lymphoma	1	5.2
Carcinoma ex-pleomorphic adenoma	1	5.2
Cystadenocarcinoma	1	5.2

Table 3. Final histopathologic diagnosis of submandibular gland lesions

	n	%
Benign (n=20)		
Pleomorphic adenoma	19	95
Non-specific chronic sialadenitis	1	5
Malign (n=7)		
Adenoid cystic carcinoma	2	28.5
Hodgkin lymphoma	1	14.2
Myoepithelial carcinoma	1	14.2
Malign epithelial tumor	1	14.2
Solitary fibrous tumor	1	14.2
Low-grade mesenchymal tumor	1	14.2

Table 4. Distribution of final histopathology in non-diagnostic FNAB cases

Final Histopathology	n, (%)
Parotid gland (n=15)	
Benign	
Pleomorphic adenoma	3, (20)
Whartin tumor	3, (20)
Lymphoepithelial cyst	2, (13.3)
Epidermoid cyst	1, (6.6)
Granulomatous sialadenitis	1, (6.6)
Castleman disease	1, (6.6)
Cavernous hemangioma	1, (6.6)
Malignant	
B-cell non-Hodgkin lymphoma	1, (6.6)
Mucoepidermoid carcinoma	1, (6.6)
Myoepithelial carcinoma	1, (6.6)
Submandibular gland (n=5)	
Benign	
Pleomorphic adenoma	1, (20)
Malignant	
Low-grade mesenchymal tumor	1, (20)
Hodgkin lymphoma	1, (20)
Adenoid cystic carcinoma	1, (20)
Solitary fibrous tumor	1, (20)

FNAB: Fine-needle aspiration biopsy

found in cystic tumors; however, no difference was found in the risk of malignancy between solid and cystic tumors ($p=0.192$).

Table 5. FNAB of solid and cystic tumors

	FNAB			Total n %
	Benign n %	Malignant n %	Non-diagnostic n %	
Solid tumors	105, 84	6, 4.8	14, 11.2	125, 100
Cystic tumors	48, 84.2	3, 5.2	6, 10.5	57, 100
Total	153, 84	9, 4.9	20, 10.9	182, 100

FNAB: Fine-needle aspiration biopsy

A total of 142 true-negatives, 8 true-positives, 11 false-negatives, and 1 false-positive case was found among the major salivary gland tumors, and the sensitivity, specificity, PPV, NPV, and accuracy of the major salivary gland FNAB in this study were 42.1%, 99.3%, 88.8%, 92.8%, and 92.5 %, respectively. The final histopathology of the only false-positive case was the Warthin's tumor, which was located in the parotid gland. Diagnostic accuracy measures among solid/cystic tumors, parotid/submandibular gland, and overall were shown in Table 6.

DISCUSSION

Salivary gland tumors are rare, mostly benign, with an annual estimated global incidence is 0.4-13.5 per 100,000 people. More than 50% of all primary salivary gland tumors occur in the major salivary glands, which are mainly present in the parotid gland, with 80%-85% being benign. Overall, tumors are more common in the parotid gland; however, the incidence of malignancy is higher in the submandibular and minor salivary glands. Histologically, the most common type of benign salivary gland neoplasms is a pleomorphic adenoma, and the most common malignant salivary gland tumors are mucoepidermoid and adenoid cystic carcinomas (3,8-10). Consistent with the literature, 85.2% of major salivary gland tumors were located in the parotid gland and 14.8% in the submandibular gland in our study. Based on final histopathology, 85.1% of 182 tumors were benign. The most common benign neoplasm is a pleomorphic adenoma and the malignant neoplasm is mucoepidermoid carcinoma.

FNAB is a safe, easy-to-apply, and inexpensive diagnostic procedure that is widely applied since the 1980s in the preoperative diagnosis of the salivary gland masses, while presenting low rates of complication and patient morbidity. However, the value of FNAB in preoperative diagnosis of salivary gland lesions is still being debated (11-13). In our study, 84% ($n=153$) of FNABs were benign, 4.9% ($n=9$) were malignant, and 10.9% ($n=20$) were non-diagnostic. Feinstein et al. (14) reported that when FNAB of the parotid gland was

Table 6. Measures of diagnostic accuracy among parotid gland, submandibular gland, solid tumors, cystic tumors, and overall

	Parotid gland	Submandibular gland	Solid tumors	Cystic tumors	Overall
Sensitivity %	43.7	33.3	45.4	37.5	42.1
Specificity %	99.1	100	99	100	99.3
PPV %	87.5	100	83.3	100	88.8
NPV %	93.1	90.4	94.2	89.5	92.8
Accuracy %	92.8	90.9	95.4	90	92.5

PPV: Positive predictive value, NPV: Negative predictive value

non-diagnostic, the final pathology was more likely benign than malignant and, when FNAB of the submandibular gland was non-diagnostic the final pathology was equally likely benign versus malignant. Similarly, when the FNAB of the parotid gland is non-diagnostic, the final histopathology was found to be most likely benign than malignant. In contrast with their findings, when the FNAB of the submandibular gland was non-diagnostic, the final histopathology was found to be most likely malignant than benign. Boursiquot et al. (7) stated that FNAB is frequently non-diagnostic in assessing cysts, as the aspirate only captures cystic fluid. In our study, similar non-diagnostic FNAB rates were found in solid (11.2%) and cystic (10.5%) tumors. This was related to our exclusion criteria of non-diagnostic cytology cases that depend on insufficient cellularity. In addition, they reported that, in line with our findings, no difference was found in the risk of malignancy between the cystic and solid tumors (7).

In the management of salivary gland tumors, distinguishing malignant tumors from benign ones is very important to determine the therapeutic approach. Olsen et al. (15) stated in their study that FNAB was found with a high false-negative rate, up to 20%, that limits its usefulness and, therefore they reported that they strictly rely on frozen section results for surgical decision making. False-negative rate was relatively small in our study, (6.7%, n=11) accounting for 20 (10.9%) non-diagnostic cases, wherein 35% (n=7) were malignant based on final histopathology.

The diagnostic value of FNAB in salivary gland tumors was assessed in several studies, and a wide range of results on accuracy for detecting malignancy was reported, with sensitivities ranging from 33% to 100% and specificities ranging from 67% to 100% (16). In the study by Kechagias et al. (4) they reported that the sensitivity and specificity of FNAB for salivary gland masses were 90% and 98%, respectively. In the study of Stow et al. (17) they reported that the sensitivity and specificity in their series were 86.9% and 96.3%, respectively. In our study, despite high specificity values, the sensitivity values for submandibular gland tumors, parotid gland tumors, cystic masses, solid masses, and overall were 33.3%, 43.7%, 37.5%, 45.4%, and 42.1%,

respectively. Therefore, despite the relatively high sensitivity values of some other studies in the literature, approximately 58% of malignant tumors of the major salivary glands were undiagnosed by FNAB in our study (4,7,12,14,17). Based on our findings, benign FNAB cytology should not be trusted and FNAB should not overcome the clinical experience and intraoperative findings. An otorhinolaryngologist should be aware of the other signs of a malignant tumor, such as anamnesis of persistent pain in the area and a rapidly growing tumor of a salivary gland.

The major limitation of this study is its retrospective nature, which included only those patients who proceeded to surgery. FNAB results could not be evaluated in terms of determining the usefulness of FNAB for patients who did not elect surgery or who pursued surgery elsewhere. In addition, the impact of different pathologists on FNAB cytology was not assessed.

CONCLUSION

Study results revealed that when the FNAB of the submandibular gland was non-diagnostic, unlike the parotid gland, the final histopathology was most likely malignant than benign. In the context of a non-diagnostic FNAB, a high suspicion for salivary gland tumors especially for the submandibular gland tumors may be warranted for otorhinolaryngologists. Similar non-diagnostic FNAB rates in solid and cystic tumors were found. Our findings demonstrated that FNAB of the parotid gland, submandibular gland, cystic, and solid masses has limitations as an only diagnostic tool. FNAB has not had a reliable sensitivity in terms of screening malignancy. For a surgeon to complement FNAB diagnosis with a patient's medical history, physical examination, own clinical experience, and radiological imaging are more appropriate.

ETHICS

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital of Local Ethics Committee (protocol number: 2020/77, date:17.02.2020).

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: F.G., M.A.A., Z.M.Y., İ.S., Concept: F.G., M.A.A., E.A., Design: F.G., E.A., Z.M.Y., Data Collection or Processing: F.G., M.A.A., E.A., Analysis or Interpretation: F.G., M.A.A., E.A., Z.M.Y., İ.B., Literature Search: F.G., E.A., İ.S., Writing: F.G., Z.M.Y., İ.S.

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