Diagnostic Efficacy of Ultrasonography-Guided Fine Needle Aspiration Biopsy in Evaluating Salivary Gland Malignancy

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Background: Salivary gland masses constitute a diagnostic challenge in daily clinical practice and tissue sampling is required to establish a diagnosis. We aimed to evaluate the efficacy of ultrasonography-guided fine needle aspiration biopsy (UGFNAB) in the diagnosis of salivary gland lesions.

Methods: From January 2007 to September 2010, a total of 158 patients who underwent both UGFNAB and surgical excision for salivary gland mass lesions were included in this study. Patients with insufficient sampling or inconclusive cytology diagnosis were excluded from the analysis of diagnostic accuracy of UGFNAB.

Results: UGFNAB yielded sufficient sampling for analysis in 137 patients, leading to a diagnostic yield of 86.7%. Among these 137 patients, 24 patients were confirmed to have malignant tumors. The sensitivity, specificity and accuracy of UGFNAB for malignancy were 66.7%, 98.2%, and 92.7%, respectively. No UGFNAB-related complications were encountered.

Conclusions: UGFNAB of salivary gland masses is a safe technique that offers high specificity and accuracy but moderate diagnostic yield and sensitivity.

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Key words: fine needle aspiration biopsy, parotid gland, salivary gland

Salivary gland swelling is a frequent complaint in daily practice and the differential diagnosis includes a long list of potential conditions. Most salivary gland tumors are benign and mainly consist of pleomorphic adenoma and Warthin's tumor. Malignant salivary tumors account for 15.7~26% of salivary gland lesions, of which mucoepidermoid carcinoma is most common, followed by adenoid cystic carcinoma, and acinic cell carcinoma.[1,2] Imaging modalities for salivary gland lesions including ultrasonography, computed tomography and magnetic resonance imaging may help to narrow the differential diagnosis. For example, although benign and malignant salivary gland tumors often have a similar sonographic appearance, several sonographic features, including a heterogeneous echotexture, indistinct margins, regional lymph node enlargement, and absence of distal acoustic enhancement,

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have been reported to be more frequently associated with malignancy.[3] Tissue diagnosis remains a standard requirement to establish a definite diagnosis. In recent years, percutaneous image-guided needle aspiration/biopsies have been increasingly used as they are less invasive than surgical biopsy. Since ultrasonography-guided fine needle aspiration biopsy (UGFNAB) offers a rapid, low cost technique for assessing the nature of salivary gland mass lesions, it is commonly used as a first-line procedure in clinical practice.[4-7] However, there is controversy about its use in the diagnosis of salivary tumors and in the determination of therapeutic management.[4-6] Reported sensitivities have varied remarkably, ranging from 55% to 94.6%.[4-6,8-14] In this study we analyzed the records of 158 patients over a 4-year period and correlated the cytological diagnoses obtained by UGFNAB with the histopathological diagnoses of surgically resected specimens. The purpose of the present study is to determine the efficacy of UGFNAB for salivary gland mass lesions.

METHODS

This retrospective cohort study was approved by the Institutional Review Board of our hospital. Informed consent was waived due to the retrospective and anonymous nature of the analysis. From January 2007 to September 2010, a total of 371 patients with salivary gland mass lesions underwent 401 UGFNAB procedures. Twenty-two patients underwent two procedures and 4 patients underwent three. The reasons for referral for UGFNAB, included a palpable mass on clinical examination in 328 patients, salivary masses incidentally found in 9 patients by computed tomography (n = 6), magnetic resonance imaging (n = 1) and ultrasound (n = 2) performed for other reasons, and a known history of salivary gland neoplasm in 23 asymptomatic patients referred for regular follow up. The remaining 11 patients with known malignancy were referred for tumor staging or postoperative follow up.

Our inclusion criterion included patients undergoing both UGFNAB and subsequent surgical resection. The exclusion criteria included patients undergoing UGFNAB only, and those undergoing subsequent incision biopsy only or core needle biopsy only. Patients with inadequate specimens for cytological diagnosis were excluded from the analysis of diagnostic accuracy of UGFNAB. For patients undergoing multiple UGFNAB procedures, the most recent cytologic diagnosis was recorded.

Sonographic examinations and biopsy procedures were performed with a real-time scanner (128X, Acuson, Mountain View, CA, U.S.A.; Sonoline Elegra, Siemens, Issaquah, WA, U.S.A.) using a 7- or 7.5-MHz linear transducer. All the fine-needle aspirations were performed under real time ultrasonography-guidance with a 21-gauge needle. For solid lesions, the aspiration was performed with a single puncture and varying angle of needle excursion on the lesion. For complex cystic lesions, the target was the solid part. If the lesion was nearly cystic, the fluid component was aspirated until total collapse of the lesion and was sent for fluid cytology. All UGFNAB specimens were alcohol-fixed and interpreted by cytopathologists. A specimen was regarded as adequate when the sample yielded sufficient materials for cytological analysis.

Salivary gland lesions were classified as benign lesions and malignant tumors. Patients with benign lesions were classified into the "negative" category while those with malignancy were classified into the "positive" category. The definite diagnoses were determined by histopathological results from surgical excision. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of UGFNAB for identification of positive lesions were calculated with standard methods using SPSS 15.0 for Windows Evaluation Version (SPSS Inc. Chicago, IL, U.S.A.).

RESULTS

Of 371 patients with salivary gland mass lesions who underwent UGFNAB, 158 patients (42.6%) underwent subsequent surgical excision and were enrolled for analysis. The other 213 patients were excluded, including 202 patients with UGFNAB only, 3 with UGFNAB and incisional biopsy, and 8 with UGFNAB and core needle biopsy. Among the 158 enrolled patients, 114 patients underwent surgical resection because neoplastic lesions were suspected on UGFNAB, while the remaining 44 patients underwent surgical resection because of persistent symptoms. There were 82 men and 76 women. Patients ranged in age from 8 to 83 years with a median of 46.5 years. Mass lesions in the parotid

gland (n = 138) were about seven-fold more common than those in the submandibular gland (n = 20). Thirteen patients had multifocal lesions. Most patients had unilateral salivary gland lesions, whereas 6 patients had bilateral parotid lesions and one had bilateral submandibular lesions.

Table 1 summarizes the UGFNAB cytological diagnoses and surgical histopathological diagnoses. UGFNAB provided cytological diagnosis in 137 of our 158 patients, resulting in a diagnostic yield of 86.7%. The remaining 21 (13.7%) patients had non-diagnostic UGFNAB specimens because of inadequate samples or inclusive cytologic resulting from low-cellularity, poor cellular quality, or presence of drying/crushing artifacts.

Among our 137 patients with diagnostic UGFNAB, the histopathological diagnosis from surgical resection showed malignancy in 24 patients, benign tumors in 101, and non-neoplastic lesions in the remaining 12. Of the 101 benign tumors, pleomorphic adenoma was the most common, followed by Warthin's tumor and basal cell adenoma. Intraparotid nodal metastasis was the most common of the 24 malignant lesion, followed by adenoid cystic carcinoma, malignant lymphoma and lymphoepithelial carcinoma. UGFNAB provided specific diagnoses in 94 (68.6%) of these 137 patients, which was concordant with the surgical histopathological results in 81 patients (Figure) but discordant in the other 13. Among the 5 patients with known metastatic lesions, UGFNAB yielded the same histopathology in 3 patients.

Table 2 summarizes the diagnostic accuracy of UGFNAB for salivary gland malignancy. For detecting malignancy, UGFNAB yielded true-positive results in 16 patients and true-negative results in 111 patients. There were a total of 10 false UGFNAB results, including 8 false-negatives and 2 false-positives. False-negatives occurred in 3 patients with adenoid cystic adenoma (misdiagnosed as pleomorphic adenoma), two patients with lymphoma (misdiagnosed as lymphoid hyperplasia in one and as negative for malignancy in the other), and one each in mucoepidermoid carcinoma (misdiagnosed as Warthin's tumor), acinic cell carcinoma (misdiagnosed as negative for malignancy) and lymphoepithelioma-like carcinoma (misdiagnosed as negative for malignancy). False-positives occurred in two patients with pleomorphic adenoma; one was incor-

Table 1. Results of UGFNAB Cytological Diagnosis and Surgery Histological Diagnosis in 137 Patients

Histopathologic diagnosis fromsurgical resection (n)	Cytologic diagnosis from UGFNAB (n)
Malignant	
Lymph node metastases (5)	PM (2), metastatic carcinoma (3)
Adenoid cystic carcinoma (4)	Pleomorphic adenoma (3), PM (1)
Lymphoma (3)	Lymphoid hyperplasia (1), PM (1), NM (1)
Lymphoepithelial carcinoma (2)	PM (2)
Mucoepidermoid carcinoma (2)	Warthin's tumor (1), PM (1)
Lymphoepithelioma-like carcinoma (1)	NM (1)
Acinic cell carcinoma (1)	NM (1)
Carcinoma ex pleomorphic adenoma (1)	PM (1)
Myoepithelial carcinoma (1)	Lymphoma (1)
Myxoid liposarcoma (1)	Myxoid liposarcoma (1)
Poorly differentiated adenocarcinoma (1)	Carcinoma (1)
Salivary duct carcinoma (1)	PM (1)
Squamous cell carcinoma (1)	PM (1)
Benign	
Pleomorphic adenoma (58)	Pleomorphic adenoma (50), NM (4), Carcinoma ex pleomorphic adenoma (1), Adenoid cystic carcinoma (1), Warthin's tumor (1), Epithelial tumor (1)
Warthin's tumor (30)	Warthin's tumor (22), NM (8)
Basal cell adenoma (6)	NM (4), Pleomorphic adenoma (2)
Lymphoepithelial cyst (3)	NM (3)
Lymphangioma (1)	Epithelial tumor with cystic changes (1)
Oncytoma (1)	Oncytoma (1)
Salivary duct cyst (1)	NM (1)
Schwannoma (1)	Pleomorphic adenoma (1)
Non-neoplastic	
Abscess (2)	NM (2)
Lymphoid hyperplasia (2)	Lymphoid hyperplasia (2)
Negative (atrophic gland) (2)	NM (2)
Acute and chronic inflammation (1) (Actinomycosis)	NM (1)
Caseating granulomatous inflammation (1)	Lymphoid hyperplasia (1)
Chronic sclerosing sialadenitis (1)	NM (1)
Fibrosis with chronic inflammation (1)	NM (1)
Lithiasis (1)	NM (1)
Sialadenitis (1)	NM (1)

Abbreviations: UGFNAB: ultrasonography-guided fine needle aspiration; PM: positive for malignancy; NM: negative for malignancy; (n) = number of patients.

rectly diagnosed as carcinoma ex pleomorphic adenoma while the other was misdiagnosed as adenoid cystic carcinoma. The sensitivity, specificity, PPV and NPV of UGFNAB for malignancy were 66.7%, 98.2%, 88.9% and 93.3%, respectively. The overall accuracy was 92.7%. There were no palpable hematomas, facial nerve palsy, infection, tumor seeding along the needle tract or any other significant post-procedural complications.

Table 2. Results of UGFNAB for Evaluating Salivary Gland Malignancy

	FNAB diagnosis		
Surgical diagnosis	Negative (Benign tumors and non-neoplastic lesions)	Positive (Malignant lesions)	Total
Negative (Benign tumors and non-neoplastic lesions)	111	2	113
Positive (Malignant lesions)	8	16	24
Total	119	18	137

Abbreviation: UGFNAB: ultrasonography-guided fine needle aspiration.
Sensitivity: 66.7%, Specificity: 98.2%, Positive predictive value: 88.9%, Negative predictive value: 93.3%, Accuracy: 92.7%.

DISCUSSION

When dealing with salivary gland lesions, the first practical problem is the distinction between benign and malignant lesions. UGFNAB for salivary gland lesions is widely accepted because it is a safe procedure for rapid diagnosis. Nevertheless, there is a wide variety of histologic types of salivary gland tumors, both benign and malignant. Owing to their histological complexity and morphologic variability, some benign and malignant salivary gland tumors share similar or overlapping cytological features.[6,12,15] The reported diagnostic sensitivities, specificities and accuracies of UGFNAB for salivary gland lesions have ranged from 55% to 94.6%, 87.7% to 100%, and 79% to 98%, respectively.[4-5,8-14,16] In our study, the accuracy and specificity were 92.7% and 98.2%, respectively, supporting UGFNAB as a highly accurate and specific method of detecting salivary gland malignancy. The sensitivity was 66.7%, falling into the lower end of the reported range.

In our series, the false-negative rate was 33.3% and the false-positive one was 1.8%. The false-negative lesions that were misdiagnosed as benign were adenoid cystic carinoma, mucoepidermoid carcinoma, acinic cell carcinoma, lymphoma, and lymphoepithelioma-like carcinoma, while the false-positive lesions were pleomorphic adenoma. On cytology, it may difficult to differentiate adenoid cystic

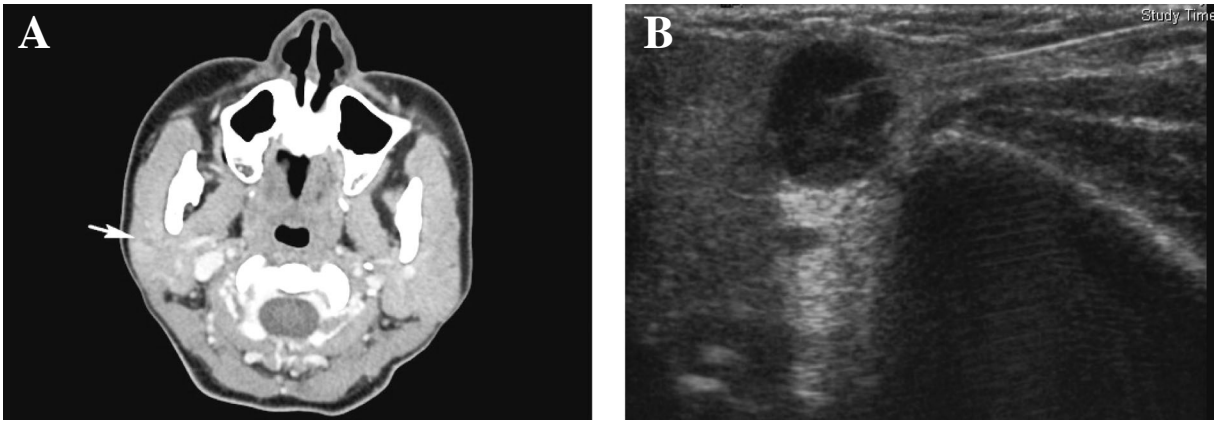

Figure (A) Post contrast enhanced computed tomography of the upper neck shows a rim- enhanced nodule (arrow) in the superficial lobe of the right parotid gland. (B) Ultrasonography-guided fine needle aspiration biopsy is performed in the heterogeneous hypoechoic nodule with a 21 G needle. The patient underwent subsequent surgical resection. Both cytology and histopathology revealed pleomorphic adenoma.

carinoma from pleomorphic adenoma,[17-19] as seen in our series in which 3 of 4 adenoid cystic carcinomas were misdiagnosed as pleomorphic adenoma while one of 58 pleomorphic adenomas was misadiagnosed as adenoid cystic carcinoma. This is because both adenoid cystic carcinomas and pleomorphic adenoma are composed of epithelial and myoepithelial cells showing minimal cytologic atypias. In addition, both lesions contain myxoid material.[6,20-22] The bland cytological features of low-grade mucoepidermoid carcinoma and acinic cell carcinoma may mimic benign lesions, contributing to incorrect cytological diagnoses. As seen in our series, one case of mucoepidermoid carcinoma was misdiagnosed as Warthin's tumor. Cytological features such as the presence of a lymphoid background, oncocytes and intermediate cells, and mucin or squamous differentiation have been documented in these two tumors.[22] Another problem in the differential diagnosis is that discrimination of lymphoma from benign lymphoid lesions can be very difficult by means of cytomorphological criteria alone.[6,8,23] Although differentiation of inflammatory disease from benign tumors is helpful in clinical management, it is difficult toachieve with UGFNAB. In our series, UGFNAB yielded just "negative for malignancy" for most inflammatory diseases and some tumors, and thus, a differentiation between benign tumors and inflammatory diseases could not be made. One area where UGFNAB is particularly helpful is in the diagnosis of metastatic lesions,[22] as seen in our series. An accurate specific diagnosis was achieved in 3 of the 5 metastases, with a diagnosis of "positive for malignancy" in the remaining 2.

Another limitation of UGFNAB is the rather high rate of unsatisfactory aspiration. About 6% to 25.5% of UGFNAB do not yield a conclusive cytological diagnosis because of insufficient cellularity or poor cellular quality, related to operator experience in performing aspiration, sampling error (needle targeting to tissue outside the lesion or a necrotic, hemorrhagic or cystic part of the tumor), technically suboptimal smears, and interpretative skills of cytopathologists.[4,5,8,11-14,16] Our UGFNAB failure rate was 13.7%, falling in the middle of the reported range. The high number of operators with various amounts of experience, might have led, at least partly, to unsatisfactory specimens in this study. If a nondiagnostic UGFNAB specimen is obtained, it is feasible to repeat the procedure with an experienced doctor and wider sampling and multiple aspirations at different sites in the lesion, particularly in circumstances in which malignancy is clinically suspected and aspiration can be well tolerated by the patient. Another means is to perform a core needle biopsy which provides an alternative choice for histopathological diagnosis apart from surgical biopsy.

Generally, large-gauge needles substantially improve diagnostic feasibility as the pathologist can more readily determine the specific type of malignant or benign mass from the larger core of tissue. Core needle biopsy aids in differentiating malignant from benign masses with reported sensitivities of 75~89%, specificities of 96.6~100%, and accuracies of 91.9~100%.[24-26] However, the risk of hemorrhage and tumor seeding might be higher than with smaller-gauge needles.[27-29] Furthermore, a target lesion size smaller than the cutting notch of the biopsy needle, as well as the proximity of the lesion to the great vessels and nerves, may preclude core needle biopsy. In contrast, UGFNAB is quicker, cheaper and less invasive than core needle biopsy.

There were no significant complications from the procedures in our series, supporting UGFNAB as a virtually complication-free diagnostic procedure. In a comparative study, Kraft found that ultrasound-guided core needle biopsy was superior to UGFNAB in the assessment of head and neck lesions because it provided a specific diagnosis (90% vs. 66%) and achieved a higher accuracy in the detection of malignancy (99% vs. 90%).[30] However, the sensitivity and specificity did not differ significantly between the two methods. They concluded that UGFNAB should continue to be the first-line investigation method for head and neck lesions.

A false-negative report is the most important issue in UGFNAC, as it may lead to incorrect and incomplete treatment of malignant disease. The considerable false-negative rate of UGFNAB for malignancy, which was 33% in this series, might suggest that UGFNAB can be used as a diagnostic tool that guides the evaluation of a salivary gland and not as an absolute histological procedure on which operative decisions can be based.[6] Therefore, although UGFNAB is still safe in the rapid diagnosis, treatment planning and follow-up of patients with salivary gland masses, management should not be entirely based on UGFNAB results because of the

risks of improper treatment and false-negative reports. Correlation of UGFNAB findings with clinical presentations as well as other imaging investigations including computed tomography, ultrasound and magnetic resonance imaging is highly recommended.

Conclusions

Our institutional experience showed that UGFNAB of salivary gland masses is a safe technique that offers high specificity and accuracy but moderate diagnostic yield and sensitivity. Recognition of its advantages and pitfalls can facilitate communication of ultrasonographers with clinicians and patients.

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超音波導引之細針吸取檢法對於診斷唾液線惡性病灶的診斷效益

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前 言： 臨床上經常會遇到因唾液腺腫塊而來求診的患者，且診斷往往要仰賴病理組織的分析。我們希望瞭解超音波導引細針吸取檢法對於唾液腺惡性病灶的診斷成效。

方 法： 本研究取樣本院自 2007 年 1 月至 2010 年 9 月止，接受超音波導引細針吸取檢法並有接受開刀治療的個案，病患數共收集 158 人，其中細胞學檢驗無法判定或採樣不足以診斷者則排除，不予列入分析其準確性。

結 果： 共計有 137 人細針吸取檢法可獲得有效的細胞學診斷，可診斷率爲 86.7%，而 137 人中有 24 人術後病理診斷爲惡性腫瘤，研究分析顯示，細針吸取檢法的敏感性、特異性、正確性分別爲：66.7%，98.2% 以及 92.7%，沒有病患因細針吸取檢法而引起併發症。

討 論： 由此研究可知唾液腺之超音波導引細針吸取檢法對是一項相當安全的檢查，它具有高特異性，但是可診斷率和敏感性並不高。

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關鍵詞： 細針吸取檢法，腮腺，唾液腺

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