RESEARCH COMMUNICATION

Accuracy of Fine Needle Aspiration Cytology of Salivary Gland Lesions: Routine Diagnostic Experience in Bangkok, Thailand

Sudarat Nguansangiam*, Somnuek Jesdapatarakul, Nisarat Dhanarak, Krittika Sosrisakorn

Abstract

Fine needle aspiration (FNA) cytology is well accepted as a safe, reliable, minimal invasive and cost-effective method for diagnosis of salivary gland lesions. This study evaluated the accuracy and diagnostic performance of FNA cytology in Thailand. A consecutive series of 290 samples from 246 patients during January 2001-December 2009 were evaluated from the archive of the Anatomical Pathology Department of our institution and 133 specimens were verified by histopathologic diagnoses, obtained with material from surgical excision or biopsy. Cytologic diagnoses classified as unsatisfactory, benign, suspicious for malignancy and malignant were compared with the histopathological findings. Among the 133 satisfactory specimens, the anatomic sites were 70 (52.6%) parotid glands and 63 (47.4 %) submandibular glands. FNA cytological diagnoses showed benign lesions in 119 cases (89.5 %), suspicious for malignancy in 3 cases (2.2 %) and malignant in 11 cases (8.3%). From the subsequent histopathologic diagnoses, 3/133 cases of benign cytology turned out to be malignant lesions, the false negative rate being 2.2 % and 1/133 case of malignant cytology turned out to be a benign lesion, giving a false positive rate was 0.8%. The overall accuracy, sensitivity, specificity, positive predictive value and negative predictive value were 97.0% (95% CI, 70.6%-99.4%), 81.3% (95% CI, 54.4%-96.0%), 99.1% (95% CI, 95.4%-100%), 92.9% (95% CI, 66.1%-99.8), 97.5% (95% CI, 92.8%-99.5%), respectively. This study indicated that FNA cytology of salivary gland is a reliable and highly accurate diagnostic method for diagnosis of salivary gland lesions. It not only provides preoperative diagnosis for therapeutic management but also can prevent unnecessary surgery.

Keywords: Salivary gland lesion - fine needle aspiration - cytology - diagnostic accuracy - Thailand

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Introduction

Salivary gland tumors are uncommon, the world wide annual incidence of salivary gland tumors ranges from 0.4 to 13.5 cases per 100 000 population (Auclair et al., 1991). Tumors of salivary glands account for 2% to 6.5 % of head and neck neoplasms and 21% to 46% are malignant (Ellis & Auclair, 1996). In Bangkok, during the period 2001-2003, the estimated age standardized incidence rate of salivary gland malignant tumor was 0.6 and 0.5 per 100,000 population for males and females, respectively (Khuhaprema et al., 2010).

Fine needle aspiration (FNA) cytology plays an important role in the evaluation of salivary gland lesions. It has been used to differentiate nonneoplastic lesions from neoplasms, and benign from malignant neoplasms (Frable & Frable, 1991; Cristallini et al., 1997; Al-Khafaji et al., 1998). It is a safe, simple, cost-effective, accurate and minimal invasive for evaluation salivary gland lesions (Frable & Frable, 1991; Layfield & Glasgow, 1991; Cajulis et al., 1997; Buley & Roskell, 2000). It is not only useful in planning definitive preoperative diagnosis but also can prevent unnecessary surgery procedures (Qizilbash et al., 1985; Layfield et al., 1987; Layfield & Glasgow, 1991; Stanley et al., 1995; Zhang et al., 2009). However, the management of patients with salivary gland lesions should not be based on cytology alone. It's superior to the combination of physical examination and radiological findings (Owen et al., 1989; Stewart et al., 2000; Kraft et al., 2008). FNA of salivary gland lesions has been performed at various institutions. Previous studies reported the diagnostic performance of FNA in salivary gland lesions; the sensitivity was in the range of 62-100%; specificity of 86-100% and accuracy of 77-98.2% respectively (O'Dwyer et al., 1986; Frable & Frable, 1991; Chan et al., 1992; Zurrida et al., 1993; Al-Khafaji et al., 1998; Boccato et al., 1998; Mihashi et a., 2006; Tan & Koo, 2006). It is widely used in America, Europe and Asia (Layfield et al., 1987; Frable and Frable, 1991; Chan et al., 1992; Zurrida et al., 1993; Stanley et al., 1995; Al-Khafaji et al., 1998; Mihashi et al., 2006; Tan & Koo, 2006). Nevertheless, this procedure has been questioned for the diagnostic value in management of salivary gland tumors and may not cost-effective in routine cytology

Department of Anatomical Pathology, Faculty of Medicine Vajira Hospital, University of Bangkok Metropolis, Bangkok, Thailand
**For correspondence: sudarat@edu.vajira.ac.th*

work for every patient (Batsakis et al., 1992; Tan & Koo, 2006).

In our institution, FNA of salivary glands are usually performed on patients during their first clinical visit and use as initial procedure for further management of the patients. Herein, we reviewed our nine - year experience in FNA cytology of salivary gland. The aim of this study was to evaluate the diagnostic performances including the accuracy of FNA for a diagnosis of salivary gland lesions in comparison to the histopathological findings.

Materials and Methods

This study was conducted after an approval from the Ethics Committee for Research involving Human Subjects of Bangkok Metropolitan Administration (registered number 093.53)The cytological reports of salivary gland FNA were retrospectively reviewed from the archive of Department of Anatomical Pathology of our institution during the nine-year period (January 2001- December 2009) and the corresponding histopathologic diagnoses were searched. We assessed the accuracy of FNA finding by comparing the cytologic diagnoses of FNA of salivary gland to the diagnoses from histopathology reports obtained with surgical excision or biopsy as the "gold standard". All cases in which cytologic diagnoses did not correlate with histopathological reports were reviewed by three experienced surgical pathologists (S.J., N.D., and K.S.) to determine sampling and interpretation errors.

In our institution, the salivary gland FNAs were performed by clinicians who responsible for preparing the slides, using 22-23 gauge needles attached to 10 mL disposable plastic syringes. The aspirated content was expressed onto two to six glass slides. The slides were immediately fixed with 95% ethanol and stained with Papanicolaou stain, except for one slide that was air-dried and stained with Diff-Quik®. Surgically excised tissue was processed routinely and the sections were stained with hematoxylin and eosin (H&E). Special stains and immunohistochemistry were used when necessary. The histological types of salivary gland tumors were established according to the WHO's Histological Classification (Barnes et al., 2005). For the purpose of this study, the FNA diagnoses were classified into four categories as follow: unsatisfactory, benign, suspicious for malignancy and malignant. Cases which were reported as unsatisfactory by FNA were not included for the analysis.

Statistical analysis

Statistical analysis to determine accuracy, sensitivity, specificity, positive predictive value, negative predictive value with their 95% confidence intervals (CI) was performed with the statistical computing programme Stata/SE 7.0 (Stata Corp., College station, TX, USA). For statistical purpose of the entire group, the suspicious and malignant cases were group together with the assumption that the suspicious cases were positive for malignancy.

Results

A total of 290 FNA of salivary glands were performed on 246 patients during the study period. There were 111 males and 135 females. The age range was 6-100 years, with a mean age of 53 years. Male: female ratio was 1: 1.2. All FNAs were performed on patients with lesions in the major salivary glands. One hundred and fifty five lesions involved the parotid gland, and 135 involved

Table 1. Comparison of Fine Needle Aspiration (FNA) Cytology and Histopathology Findings (n=133)

FNA	Histopathology		
	Benign	Malignant	Total
Benign	116 (TN)	03 (FN)	119
Suspicious	000 (FP)	03 (TP)	3
Malignant	100 (FP)	10 (TP)	11
Total	117	16	133

FN=false negative; FP=false positive; TN=true negative, TP=true positive

Table 2. FNA Diagnoses correlated with Benign Histopathologic Diagnoses (n=117)

Histopathologic diagnosis	No. of case	FNA diagnosis			
		B[a]	B[b]	S[c]	M[d]
Benign neoplasms (48)					
Pleomorphic adenoma	34	-	34	-	-
Warthin's tumor	13	-	13	-	-
Basal cell adenoma	1	-	1	-	-
Benign non-neoplasms (69)					
Sialadenitis/abscess/necrotizing	58	57	-	-	-
Lymphoid hyperplasia	5	5	-	-	-
Benign lymphoepithelial lesion	2	2	-	-	-
Benign cyst	2	2	-	-	-
Sialolithiasis	1	1	-	-	-
No remarkable change	1	1	-	-	-
Total	117	68	48	-	1

[a]Benign non-neoplasm; [b]Benign neoplasm; [c]Suspicious; [d] Malignant

Table 3. FNA Diagnoses Correlated with Malignant Histopathologic Diagnoses (n=16)

Histopathologic diagnosis	No. of case	FNA diagnosis		
		B[a]	S[b]	M[c]
Malignant neoplasms				
Malignant lymphoma	4	2	2	-
Mucoepidermoid carcinoma	3	-	1	2
Squamous cell carcinoma	2	-	-	2
Adenocarcinoma, NOS	1	1	-	-
Carcinoma ex pleomorphic adenoma	1	-	-	1
Salivary duct carcinoma	1	-	-	1
Large cell undifferentiated carcinoma	1	-	-	1
Metastatic carcinoma	3	-	-	3
Total	16	3	3	10

[a]Benign; [b]Suspicious; [c]Malignant

Table 4. Diagnostic Performance of Fine Needle Aspiration Cytology of Salivary Gland Lesions (n=133)

Parameter	Values (%)	95% CIs
Accuracy	97.0	(70.6-099.4)
Sensitivity	81.3	(54.4-096.0)
Specificity	99.1	(95.4-100.0)
Positive predictive value	92.9	(66.1-099.8)
Negative predictive value	97.5	(92.8-099.5)

CIs, confidence intervals

the submandibular gland. The size of the lesions was ranged from 0.5 to 12 cm in diameter with a mean size of 2 cm. One hundred and forty two FNAs diagnoses were excluded because no surgery was performed in these cases (lack of the final histopathological diagnoses). Fifteen of 290 specimens (5.2%) were unsatisfactory because they contained no cells or only blood on smears. Therefore, 133 specimens were analyzed. Among 133 satisfactory specimens verified by histopathological diagnoses, the anatomic sites of the aspiration were 70 (52.6%) parotid glands and 63 (47.4 %) submandibular glands. FNA cytological diagnoses showed benign lesions in 119 cases (89.5 %), suspicious for malignancy in 3 cases (2.2%) and malignancy in 11 cases (8.3%). The final histopathological diagnoses showed 117 (88%) benign lesions and 16 (12%) malignant neoplasms. The comparison results are shown in Table 1.

Table 2 lists results for the 117 benign lesions (48 benign neoplasms and 69 benign non-neoplsms). In our study, the rate of agreement between FNA and histopathogical diagnoses of benign neoplasms was excellent (100%). Pleomorphic adenoma was the most common salivary gland neoplasm accounting for 53% (34/64) of all neoplasms and 70.8% (34/48) of the benign neoplasms. Warthin's tumor was the second most common salivary gland neoplasm accounting for 20.3% (13/64) of all neoplasms and 27.1% (13/48) of the benign neoplasms. For benign non-neoplasm , only one case was misdiagnosed cytologically as "squamous cell carcinoma" and was histologically proved to be necrotizing sialadenitis. The false positive rate for histologically proven benign lesions was 0.8% (1/133).

Table 3 lists results for the 16 malignant neoplasms. Thirteen (81%) were primary malignant neoplasm of salivary gland, 3 (19%) were metastatic malignant neoplasms. The three cases in which FNA cytology was suspicious for malignancy were histologically proved to be malignant in all cases (two lymphomas and one mucoepidermoid carcinoma). Nevertheless, the three cases in which FNA cytology was benign lesions were histologically proved to be malignant. These include two cases of lymphoma misdiagnosed as reactive lymphoid hyperplasia and one case of adenocarcinoma misdiagnosed as negative for malignancy. When the suspicious and malignant cases were grouped together, the false negative rate for histologically proven malignancies was 2.2% (3/133). In this study, malignant lymphoma and mucoepidermoid carcinoma were the most common primary malignant neoplasms, which accounted for 25 % (4/16) and 18.8% (3/16) of all malignant neoplasms. For the entire group, the overall accuracy, sensitivity, specificity, positive predictive value and negative predictive value of FNA of salivary glands are summarized in Table 4.

Discussion

The results of our study indicated that FNA biopsy is a safe, simple and effective diagnostic method in the management of patients of salivary gland lesions. In our institution, FNA is routinely used as a practical method for a preoperative diagnosis of salivary gland lesions and usually performed during the patient's first clinical visit. During the 9-year period of this study, 290 specimens of FNA cytological diagnoses of salivary glands were reviewed, 142 specimens did not have histopathological reports, which may be because they were verified as benign lesion and got no evidence of tumor cells by FNA cytology diagnoses. FNA provides beneficial preoperative information for help the clinician in deciding whether a particular patient should be managed surgically. Previous study reported that using FNA as an initial diagnostic tool have been able to reduce the number of operative procedures on salivary gland lesions approximately 30% (Qizilbash et al., 1985) and some patients do not receive invasive treatment (Mavec et al., 1964). The unsatisfactory specimens in this study was 5.2% which was relatively low as had been reported in the literatures (Cadillo, 1990; Layfield & Glasgow, 1991; Jayaram et al., 1994; Boccato et al., 1998; Tan & Koo, 2006; Mihashi et al., 2006, Jan et al., 2008), vary from 3% to 12%. The difference range may occur from sampling method, experience of clinician who perform adequate specimen, without the aid of cytopathologist (Boccato et al., 1998). However, in our institution, the procedure was assessed by experience clinician or resident in training under a close supervision of the expert and the aspirations were prompt submitted to the Anatomical Pathology Department after the procedure.

In our study, the diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of preoperative FNA cytology of salivary gland lesions were 97%, 81.3 %, 99.1%, 92.9%, and 97.5% respectively, indicating good results compared with those previously reported from other institutions (O'Dwyer et al., 1986; Frable & Frable, 1991; Chan et al., 1992; Zurrida et al., 1993; Al-Khafaji et al., 1998; Boccato et al., 1998; Mihashi et al., 2006; Tan & Koo, 2006). Nevertheless, other studies have reported wide variation in sensitivity and specificity of FNA cytology of salivary gland in detecting malignant tumors, ranging from 29% to 97% and 84% to 100%, respectively (reviewed in Cohen et al., 2004). Factors contributing to a wide range are unclear, but they may be related to technical factor, experience of clinician performing the FNA and experience of cytopathologist (Cohen et al., 2004).

The rate of benign non-neoplasm lesion in this study was 51.9%. It is in keeping with those of other studies, range from 20% to 72.9% (Chan et al., 1992; Atula et al., 1996; Cajulis et al., 1997; Boccato et al., 1998; Das et al., 2004). The high proportion of benign non-neoplasm lesion was inflammatory lesion and reactive lymphoid hyperplasia. Some authors concluded that the high proportion of inflammatory lesion may be due to geographical differences (Cajulis et al., 1997; Yang & Kuhel, 1997; Das et al., 2004). The rate of agreement between FNA and histopathogical diagnoses of benign neoplasm in this study was excellent, at 100%. The most common benign neoplasm was pleomorphic adenonoma which accounted for 53% of all neoplasms and Warthin's tumor was the second most common (20.3%). The predominance of these two benign neoplasms was similar to those previously reported in a number of studies (Cajulis

et al., 1997; Cristallini et al., 1997; Frable & Frable, 1991; Chan et al., 1992; Das et al., 2004, Mihashi et al., 2006).

In this study, malignant neoplasms accounted for 16 cases (12%). The rate of malignant neoplasm was lower than other reports which ranged from 15% to 32% in an unselected population (Chan et al., 1992; Zurrida et al., 1993; Jayaram et al., 1994; Atula et al., 1995; Atula et al., 1996; Cajulis et al., 1997; Boccato et al., 1998; Wong & Li, 2000; Hee & Pery, 2001). The lower rate of malignant neoplasms may result from rare incidence of salivary gland malignant neoplasms in our country (Khuhaprema et al., 2010). The most common primary salivary gland malignant tumors were lymphoma (25%, 4/16) and mucoepidermoid carcinoma (18.8 %, 3/16). The high rate of malignant lymphoma is similar to previous studies (Chai et al., 1997; Al-Khafaji et al., 1998; Cohen et al., 2004).

The reported incidence of secondary malignant neoplasms ranged from 1% to 24% involving the major salivary gland (Gnepp, 1991). In our study, it accounted for 2.2% (three cases). Metastatic carcinomas were mainly from squamous cell carcinoma of larynges (two cases) and undifferentiated carcinoma of nasopharynx (one case). The majority of metastases were arising in the head and neck region as well as in the series of others (Seifert et al., 1986; Gnepp, 1991; Zhang et al., 2000). Previous studies found that most of metastases to salivary glands develop from primary squamous cell carcinoma of the skin (head and neck) or from melanomas of this region but hematogeneous metastases are relatively rare and mainly from the lung, kidney and breast (Seifert et al., 1986; Gnepp, 1991). We agree that it is important to differentiate a primary neoplasm from a secondary malignant neoplasm to avoid unnecessary surgery and to guide subsequent management but the distinction between primary and secondary squamous cell carcinoma on cytology alone is impossible. The clinical history and the previous histopathological reports can be helpful for indicating as metastases neoplasms (Klijanienko & Vielh, 1998; Zhang et al., 2000).

Although the three suspicious cases of our study were correct diagnosed and turned out to be two lymphomas and one mucoepidermoid carcinoma. Repeat aspiration of suspicious cases is highly recommended. We strongly believe that even though the fine needle aspiration give a suggestive diagnosis of lymphoma, we should confirm by surgical biopsy and further study of immunohistochemistry which can be helpful for these cases. Furthermore, it is difficult to diagnose mucoepidermoid carcinoma because it occurs in low and high grade forms and it is easier to diagnose high grade than low grade form. Low grade mucoepidermoid carcinomas may be misdiagnosed as chronic sialadenitis, mucous retention cyst, Warthin's tumor, and adenomatoid hyperplasia of the mucous salivary gland (reviewed in Layfield and Glasgow, 1991) and the cells may not show significant pleomorphism for diagnosing malignancy. Thus, we should careful examine of these smears to prevent false negative results.

When the suspicious and malignant cases were grouped together, the false positive in our study was 0.8% (one case), which was within the range reported in the other studies, 0 - 4.7% (Qizilbash et al., 1985; O'Dwyer et al., 1986; Chan et al., 1992). The one false positive case histologically proved as necrotizing sialadenitis and misdiagnosed as squamous cell carcinoma. The cause of misdiagnosis was error in interpretation. When we reviewed these slides, there were some clusters of atypical squamous cells with nuclear atypia on the necrotic background. Thus, we should concern that both neoplasm and nonneoplasm lesions of salivary gland may contain squamous cells which occasional unexpected findings and it may be the cause of potential misdiagnosis (Mooney et al., 1996). Some authors found that true squamous cell carcinoma generally yield more cellular smears with many single malignant cells rather than tightly cohesive aggregates (Layfield & Glasgow, 1991).

The false negative rate in this study was 2.2 % (three cases) which was low in the range as had been reported in the previous studies, ranged from 4.7% to 24.5% (O'Dwer et al., 1986; Layfield et al., 1987; Chan et al., 1992; Orell, 1995; Stewart et al., 2000). The three false negative FNA results were two lymphomas, and one adenocarcinoma. Both cases of lymphoma were primary lymphomas of the salivary gland tumors and misdiagnosed as reactive lymphoid hyperplasia. The final histopathological reports were low grade non-Hodgkin's B-cell lymphoma and follicular lymphoma. The role of FNA in the diagnosis of lymphoma is controversial. The College of American Pathologists (CAP) Interlaboratory Comparison Program in Nongynecologic Cytology (NGC) reported that malignant neoplasms cases of salivary gland with the highest false-negative rates were lymphoma, acinic cell carcinoma, low-grade mucoepidermoid carcinoma, and adenoid cystic carcinoma (Hughes et al., 2005). It is difficult in diagnosis low grade lymphoma based on FNA alone. Lymphoma may involve the salivary glands or intraparotid lymph nodes and pose problem in diagnosis. The differential diagnosis includes reactive lymphoid hyperplasia, benign lymphoreticular lesion, chronic sialadenitis and adenolymphoma (Qiziblash et al., 1985). When we reviewed these slides, we found that these cases were due to error in interpretation. For lymphoma cases, the smears of low grade non-Hodgkin's B-cell showed small and large lymphocytes with round nuclei and mild atypical nuclei. The smears of follicular cell carcinoma showed predominantly small lymphocytes, scattered with histiocytes and some tangible body macrophages. This may lie with the reason that lymphoma may arise in a background of a reactive lymphoid proliferation, sometime may contain a mixed population of lymphoma cells and benign inflammatory cells, as well as lack of cellular atypia, makes this diagnosis difficult by cytology alone and leading to an erroneous diagnosis of the reactive process (Qiziblash et al., 1985; O'Dwyer et al., 1986; Zurrida et al., 1993; Cohen et al., 2004). Such false negative cases may result from experience, the more experience cytopathologist, the more improves diagnosis accuracy (O'Dwer et al., 1986). High grade lymphomas are easier to diagnose than low grade lymphomas. The FNA specimen with predominantly lymphocytes without salivary epithelium was frequently associated with low-grade lymphoma on final histological diagnosis in both

suspicious and malignant cytological diagnosis so it should prompt further study for lymphoma (Cohen et al., 2004). FNA cytology along with various ancillary studies, such as immunocytochemistry and flow cytometry can be helpful to diagnostic and classification lymphomas and separate them from reactive hyperplasia (Stewart et al., 1998; Dong et al., 2001). One adenocarcinoma case was misdiagnosed as negative for malignancy. Retrospective review showed scant normal salivary gland tissue, but no tumor cells. Sampling error is the major factor that led to false-negative result in this case. We agree with prior studies that the sufficient specimen can improve the diagnostic accuracy (Jayaram et al., 2004; Mihashi et al., 2006). Recently study concluded that there were four reasons for incorrect interpretation in cytological diagnosis of salivary gland including inadequate sampling or insufficient specimens, marked cellular degeneration, error of labeling specimens and cytologist unfamiliar with the morphology of rare salivary gland lesion (Jan et al., 2008).

Other essential tool in the management of salivary gland lesions is intraoperative frozen section (FS). FS analysis of salivary gland tumors has traditionally been used to identify or exclude malignancy and to type the salivary gland lesion. Some authors advocated that FS is superior to FNA for the reason that FNA cannot be relied upon to type or grade malignant salivary gland tumors and FNA should not be used as the sole determinant of surgical management for primary parotid carcinomas (Zbaren et al., 2004). Whereas, some studies found that FNA is more sensitivity, FS is more specific but both FS and FNA provide a similar accuracy (Layfield et al., 1987; Seethala et al., 2005). Some authors concluded that FNA and FS are complementary in usefulness for malignant tumors of salivary gland lesions but FNA do not influence the management of benign lesions and routine FNA for every patient may not be cost-effective (Tan & Koo, 2006). However, we agree that both modalities are very useful for assessing the salivary gland lesions which suspected to be malignant on clinical or radiological findings.

In summary, our study shows the high accuracy, sensitivity and specificity and do confirm that FNA of salivary gland lesions is a valuable diagnostic tool in the workup of patients with salivary gland lesions. Many patients are saved the necessity of surgery. It is simple, accurate and cost effective method so it is suitable for developing countries with low financial resources. For these reasons, FNA should be part of the initial evaluation of patients with major salivary gland lesions. However, we should realize that false positive and false negative results will always occur. We agree with the recommendation that use of FNA in combine with clinical examination and radiological findings (the triple test) approach similar to that used in FNA of breast lesion would protect false negative and false positive diagnoses and provide valuable and accurate diagnosis in the investigation of salivary gland lesions.

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