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ORIGINAL ARTICLE

Fine-needle aspiration cytology of salivary gland tumours: a 10-year retrospective analysis

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Abstract
Introduction The aim of this study was to evaluate the sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) of fine-needle aspiration cytology (FNAC) of salivary gland tumours performed at a tertiary cancer hospital over a time period of 10 years.
Materials and methods A retrospective analysis was carried out between 1995 and 2004 to review the cases of patients with salivary gland tumours who had undergone pre-operative FNA and for whom definite histology was either by tru-cut biopsy or by histopathological examination of the operative specimen.
Results A total of 107 cases of salivary gland tumours were treated during that period, but only 82 cases diagnosed by FNAC could be correlated with histological and clinical data and were considered for this study. The sensitivity, specificity, diagnostic accuracy, PPV and NPV were estimated considering 54 benign and 28 malignant cases. Sensitivity was 90% (28/31), specificity was 98% (54/55), diagnostic accuracy was 95.1% (82/86), PPV was 96% and NPV was 94%.
Discussion This study confirms that FNA cytology is a technique that offers high sensitivity, specificity and diagnostic accuracy in salivary gland tumour diagnosis.

Keywords Salivary gland tumour · Fine-needle aspiration cytology

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Introduction

Fine-needle aspiration cytology (FNAC) is a safe and reliable procedure for the diagnosis of salivary gland lesions. It is simple, well tolerated and can be easily repeated if a second sample is required. The main advantage is the possibility of a fast clarification of a diagnostic dilemma, by distinguishing between a systemic disease, a benign lesion or a malignancy. FNAC has been used for many years [1]; nevertheless, controversial opinions about its value as a diagnostic method still exist, and the indications for its use remain undefined [2]. It has been suggested that this could be explained by slow accrual due to paucity of presentation of salivary gland masses in most medical centres, the consequent lack of expertise of many cytopathologists and the retrospective nature of studies reported to date [3]. Although a high sensitivity and specificity of FNA has been reported [4], the technique is largely operator sensitive [5].

Our experience as a tertiary care cancer centre showed that FNAC is a valuable first-line diagnostic tool especially for patients with salivary gland tumours, as a quick and

easily reproducible means of obtaining pre-operative diagnosis to guide ultimate surgical planning. To assess the diagnostic accuracy of this technique in direct comparison with histopathological analysis as the gold standard, we retrospectively analysed all lesions of the parotid, the submandibular and the minor salivary glands that were treated over a time period of 10 years in our institute.

Materials and methods

This study is part of a large retrospective analysis assessing the surgical activity of the Department of Oral and Maxillofacial Surgery of the Theagenion Cancer Hospital of Thessaloniki, Greece, for the decade 1995–2004. In this period, a total of 107 patients with salivary gland lesions were treated. Adequate FNAC, histological and clinical data for correlational analysis were available in 82 cases.

All FNA procedures were performed by dedicated cytopathologists. In all cases, a 21-gauge needle was used, attached to a 10-ml syringe. Two or more passes were performed, and the material was processed using the conventional, as well as liquid-based cytology (ThinPrep) technique. The smears were stained according to the Papanicolaou procedure. In selected cases, to aid diagnosis, immunocytochemistry using specific monoclonal antibodies followed. The cytological features of the salivary gland lesions and the distribution of these lesions in the major and minor salivary glands are described.

Cytopathological and histological findings were categorised as benign and malignant. Sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value were calculated using histological diagnosis of the surgical specimen or the tru-cut biopsy report, as the standard criterion. Sensitivity was calculated on the basis of the ratio of positive tumours to all tumours confirmed to be malignant. Specificity was calculated as the ratio of tumours with negative results to all tumours confirmed to be nonmalignant. Diagnostic accuracy was calculated by dividing the total number of true-positive and true-negative tumours by the total number of tumours. Positive predictive value was calculated by dividing the total number of true-positive and the total number of true-positive plus false-positive tumours, while negative predictive value was calculated by dividing the total number of true-negative and the total number of true-negative plus false-negative tumours. All cases in which cytopathology did not correlate with histology were reviewed by a cytopathologist to identify whether specimen quality or sampling error may have contributed to this lack of correlation.

Results

From a total of 107 patients with salivary gland lesions, FNA results could be compared to available histological findings from tru-cut biopsies and/or operative specimen analysis in 82 cases (76.6%). All other cases were excluded from this analysis. There were 62 men and 20 women, with a male-to-female ratio of approximately 3:1 (76% vs. 24%). The ages of the patients ranged from 27 to 84 years, with a mean age of 56.8 years. The samples were obtained from the parotid in 52 cases (63.4%), the submandibular in 25 cases (30.5%) and the minor salivary glands in 5 cases (6.1%) (Table 1). Of the benign lesions, 66.6% were in the parotid and 24.1% in the submandibular gland. Approximately 70% of all tumours of the parotid gland were benign and 30% malignant, whereas in the submandibular gland, 52% were benign and 48% malignant tumours. Our series includes five cases of minor salivary gland lesions, one located in the upper lip, two in the buccal mucosa and two in the palate, all ultimately diagnosed as Warthin's tumours.

Cytology diagnoses were coded as (a) inadequate, (b) negative for malignancy, (c) benign lesion, (d) suspicious and (e) positive for malignancy. The results of the FNA cytology diagnosis are summarised in Table 2.

In total, there were 54 benign lesions (65.85%) and 28 malignant (34.15%) lesions. In four cases (7.4%), the samples were inconclusive for diagnosis (Table 2). We had no suspicious cases in our series. The most frequently occurring benign tumours were Warthin's tumour (50%) and the pleomorphic adenoma (33%). Twenty-eight malignant salivary gland tumours were encountered in the series, comprising 20 primary neoplasms (71.4%) and 8 metastatic lesions (28.6%). The most frequent malignancy was adenocarcinoma: eight (32.3%, Fig. 1). The remaining primary malignancies were three squamous cell carcinomas (10.8%), two mucoepidermoid carcinomas (7.2%, Fig. 2), one anaplastic carcinoma (3.6%) and five non-Hodgkin's lymphomas (17.5%). The metastatic tumours were squamous cell carcinomas originating from head and neck primaries.

Table 1 Distribution of the lesions in the different anatomic sites

	Benign	Malignant	Total
Parotid	36	16	52
Submandibular	13	12	25
Minor salivary	5	–	5
Total	54	28	82

Table 2 Results of FNA cytology in 82 cases

Benign lesions	Number of cases	Malignant lesions	Number of cases
Inadequate for diagnosis	4	Adenocarcinoma	9
Inflammation	5	Mucoepidermoid carcinoma	2
Pleomorphic adenoma	18	Anaplastic carcinoma	1
Warthin's tumour	27	Squamous cell carcinoma (SCC)	3
		SCC metastasis	8
		Non-Hodgkin lymphoma	5
Total	54	Total	28

The sensitivity, specificity and diagnostic accuracy were estimated considering the 82 cases for which FNAC data could be fully correlated with histological data. Based on the above, sensitivity was estimated at 90% (28/31) and specificity at 98% (54/55), diagnostic accuracy was 95.1% (82/86), PPV was 96% and negative predictive value (NPV) was 94%.

In seven cases (8.5%), there was discordance between the FNA cytology and the definite histological diagnosis (Table 3). In cases no. 3 and 4, the FNAC was inadequate for diagnosis; a NOS adenocarcinoma and a myoepithelial carcinoma respectively were diagnosed by histology. In case no. 5, salivary gland tuberculosis was initially diagnosed as Warthin's tumour by FNA (Fig. 3). However, because of the vague imaging findings and the clinical suspicion, an imaging-guided biopsy with a tru-cut needle was performed, and the infectious disease was documented. In case no. 6, a squamous cell carcinoma was diagnosed as a mixed tumour by FNA, and in case no. 7, a Warthin's tumour was over-interpreted as a squamous cell carcinoma by cytology (Fig. 4).

Discussion

Theagenion Cancer Hospital is a tertiary care cancer centre, managing a large number of patients with salivary gland tumours presenting or referred to our department.

FNAC is a valuable tool in the diagnosis of head and neck lesions with a proven high diagnostic accuracy [1, 4, 5]. This is particularly true for salivary gland neoplasms because the clinician is guided by FNA diagnosis in deciding about the management of patients. In the vast majority of patients, careful interpretation of the cytomorphologic findings renders an accurate diagnosis, allowing for conservative management of patients with benign lesions [5].

Biopsy with tru-cut needle had selectively been used following FNAC in cases of doubt, when a non-salivary malignancy or systemic disease was suspected. No precise criteria exist for the selection of patients who undergo this procedure. It depends mainly on the surgeon's needs for clarification of clinical questions and to enable optimised pre-operative patient information and consent. Core biopsy

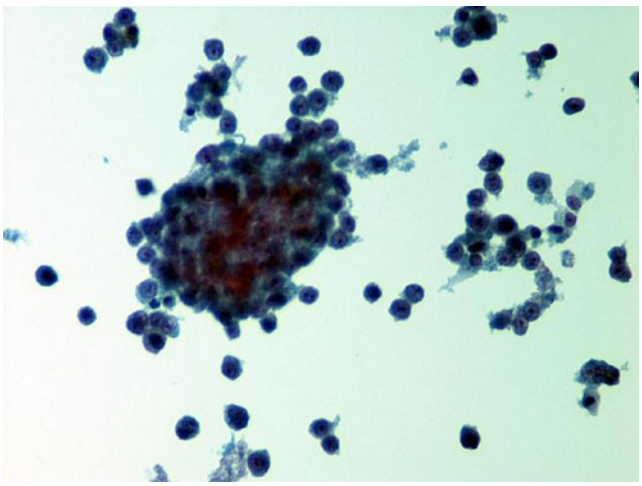

Fig. 1 Adenocarcinoma (ThinPrep; Pap stain, ×400)

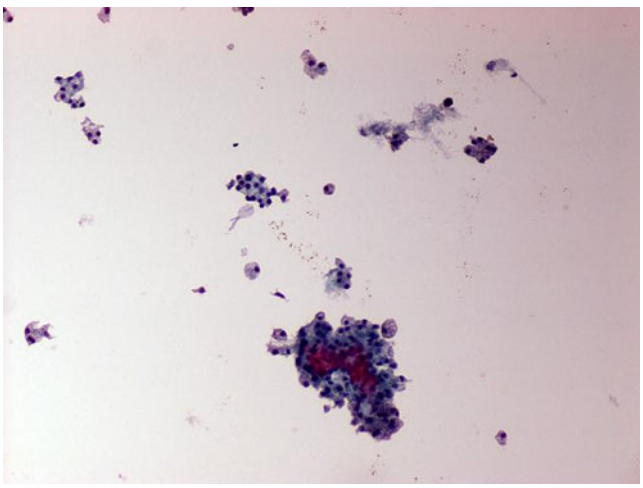

Fig. 2 Mucoepidermoid carcinoma (ThinPrep; Pap stain, ×200)

Table 3 Cases with discordance between cytological and histological diagnoses

Number of cases	Cytology	Histology
1	Inflammation	Pleomorphic adenoma
2	Inadequate for diagnosis	Warthin's tumour
3	Inadequate for diagnosis	NOS adenocarcinoma
4	Inadequate for diagnosis	Myoepithelial carcinoma
5	Warthin's tumour	Tuberculosis
6	Pleomorphic adenoma	Squamous cell carcinoma
7	Squamous cell carcinoma	Warthin's tumour

is also indicated for the diagnosis of haematological malignancies. All of our lymphoma cases subsequently underwent core biopsy, in order to obtain adequate tumour volume for precise diagnosis and typing. It is our opinion, however, that lymphoma cases of the salivary glands are not that frequent to justify systemic use of tru-cut biopsy as a first-line diagnostic tool, unless there is a strong suspicion given the clinical context.

The distribution between the different anatomical sites of the salivary gland lesions in this retrospective study is similar to what has previously been reported, with the parotid gland being the most commonly affected site [6, 7]. It is of interest, however, that the most frequently diagnosed benign tumour in our series is not pleomorphic adenoma, as traditionally reported, but Warthin's tumour.

When considered from the viewpoint of type-specific diagnostic accuracy of tumours, the sensitivity of FNAC reaches approximately 80% and is better for benign than malignant neoplasms. Diagnosis of pleomorphic adenoma is invariably high [8, 9], but mucoepidermoid carcinoma and carcinoma ex-pleomorphic adenocarcinoma [10] can pose problems for even the most experienced, as will the unexpected encounter of a rare tumour. Accurate subtyping of salivary gland malignancies is a well-known diagnostic challenge because the histopathology of these tumours is extremely varied and complex. The low-grade tumours especially can mimic normal tissue or benign lesions [11].

In our series, we encountered difficulties with NOS adenocarcinomas and anaplastic carcinomas because they presented with no specific cytologic features, in order to include them in the well-known categories. The mucoepidermoid carcinomas and squamous cell carcinomas (SCCs) (primaries or metastatic) were quite typical, and also the NH-lymphomas, a frequent diagnosis in our series, were accurately diagnosed by the presence of a monomorphous population of small (MALT lymphoma) or large-sized (high-grade lymphoma) lymphoid cells with irregularly clumped chromatin and irregular nuclear membrane, as described by others [3]. Also, immunocytochemistry using the appropriate antibodies (LCA, anti-B cells, anti-T cells) supported our diagnoses.

The seven discordant cases were carefully re-examined. In three cases with histological diagnosis of Warthin's tumour, adenocarcinoma and myoepithelial carcinoma, inadequate cytological material was obtained, which is not uncommon especially when cystic necrosis in Warthin's tumour or in carcinomas is present. In another case, which was proven to be a pleomorphic adenoma, only inflammatory cells were present on cytology smears. One case of tuberculosis was diagnosed as Warthin's tumour on cytology, because of the great amount of lymphocytes and the sparse presence of epithelial cells with oncocytic metaplasia, probably due to the inflammation.

On the other hand, a case of Warthin's tumour was overdiagnosed as a squamous cell carcinoma because the smears contained necrotic or cellular debris due to cystic

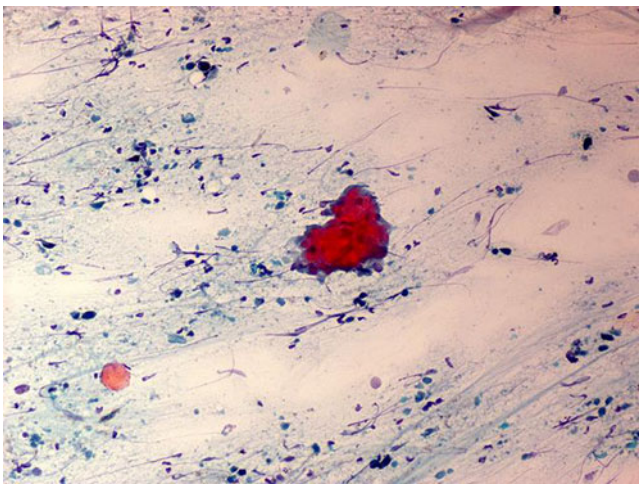

Fig. 3 Tb inflammation (conventional; Pap stain, ×200)

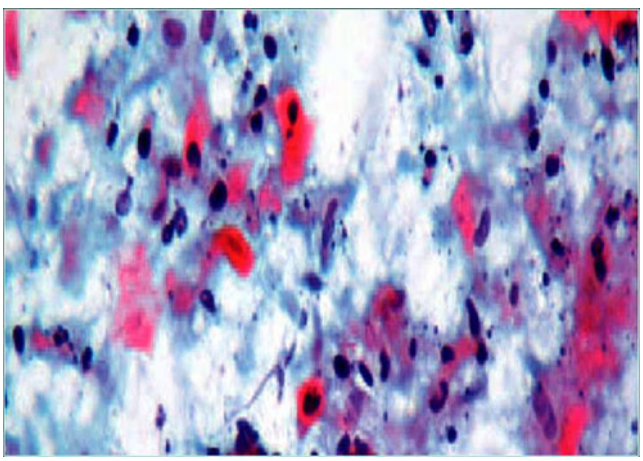

Fig. 4 Warthin's tumour with keratinized squamous cells (conventional; Pap stain, ×200)

necrosis, with the presence of small keratinised squamous cells. This is one of the common "false-positive" misinterpretations of Warthin's tumour, well described in the literature [12]. In actual fact, the often variegated cytomorphology of Warthin's tumour may frequently lead to an erroneous cytopathologic interpretation.

Finally, one case of cytologically diagnosed pleomorphic adenoma turned out to be a squamous cell carcinoma on histology. In this case, FNA failed to collect malignant cells from the neoplastic area, and only normal salivary gland tissue was present on review.

In the current series, the diagnostic accuracy of FNA of salivary gland tumours was 95.1%; the sensitivity, 90%; the specificity, 98%; the PPV, 96% and the NPV, 94%. Our results are similar to those previously reported in other studies [2, 13, 14].

We must emphasise the point that high diagnostic accuracy is related to well-experienced cytologists, who perform the FNAs themselves, smear the slides or follow the liquid-based cytology procedures. Over- or misinterpretation may occur due to an overabundance of atypical features, necrotic background, inflammation and/or lack of typical cytological characteristics of salivary gland tumours.

Therefore, an awareness of these potential sources of erroneous diagnoses is essential in order to achieve higher accuracy rates and more appropriate therapeutic management by the clinicians. Ways of optimising the diagnostic accuracy of FNAC include experienced operators; ideal, reproducible sampling technique and imaging-guided sampling (usually ultrasound-guided) in cases of large, heterogeneous tumours and/or difficult-to-access tumours.

The diagnostic value of FNAC in salivary gland pathology, alone or in comparison to other diagnostic modalities, has been assessed in several studies, including a large recent systematic review [11]. They have all confirmed its high sensitivity (between 75% and 100% for most, although there were reports of sensitivity as low as 64%. Sensitivity and specificity are higher for benign tumours, decreasing in cases of malignant tumours [13]) and specificity between 87% and 100% [3, 8, 11, 15–18].

The sensitivity, specificity and diagnostic accuracy of FNAC were compared with those of MRI specifically in the diagnosis of salivary gland tumours [16, 19]. Sensitivity alone was better for MRI, reaching 100% with the combination of the two techniques. It should be noted, however, that FNAC was shown superior to MRI in terms of both specificity and diagnostic accuracy [16, 19]. Similarly, FNAC showed higher specificity and diagnostic accuracy to computed tomography (CT) in the diagnosis of parotid tumours, but lower sensitivity [16]. In our series, although all patients had salivary gland imaging (usually by CT), given the cost-effectiveness considerations that apply in the context of national health system services, MRI was not justified as a routine first-line diagnostic tool.

It has also been suggested that pre-operative FNAC can be combined with intra-operative frozen section to define the extent of parotidectomy, need of neck dissection or even advanced radical parotidectomy [3]. However, other authors reporting on the use of intra-operative frozen sections have reported lower true-positive and higher false-negative rates compared with FNAC [18]. In our centre, the use of intra-operative frozen sections is limited, as we do not frequently perform pericapsular excisions or other minimally invasive techniques where the use of frozen sections might be indicated. In cases of two subsequent failed FNAs, and if core biopsy is not indicated or is technically difficult to perform (e.g., small tumours), taking in consideration clinical and imaging data, we perform complete gland excision respecting oncological safety rules.

In conclusion, FNA biopsy is a simple and valuable tool for the correct pre-operative distinction between benign or systemic diseases and malignancies in the outpatient setting, in order to avoid unnecessary surgery, e.g., for a haematological malignancy that ought to be managed differently. Furthermore, pre-operative prediction of histological subtype aids in the treatment planning and surgery design in relation with tumour pathology, relapse risk, etc. The choice of FNA as a first-line diagnostic tool aids to avoid nerve damage, decrease the risk for tumour spillage, avoid unsightly biopsy scars, etc., entailing however the small but not inexistent risk for diagnostic errors compared to histology.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cohen MB, Reznicek MJ, Miller TR (1992) Fine-needle aspiration biopsy of the salivary glands. PatholAnnu 27:213–245
2. Stewart CJ, MacKenzie K, McGarry GW, Mowat A (2000) Fine-needle aspiration cytology of salivary gland: a review of 341 cases. Diagn Cytopathol 22(3):139–146
3. Carrillo JF, Ramirez R, Flores L, Ramirez-Ortega MC, Arrecillas MD, Ibarra M, Sotelo R, Ponce-de-Leon S, Onate-Ocana LF (2009) Diagnostic accuracy of fine needle aspiration biopsy in preoperative diagnosis of patients with parotid gland masses. J Surg Oncol 100:133–138
4. Riley N, Allison R, Stevenson S (2005) Fine-needle aspiration cytology in parotid masses: our experience in Canterbury, New Zealand. ANZ J Surg 75:144–146
5. Gal R (1996) Fine needle aspiration of the salivary glands: a review. Oper Tech Otolaryngol Head Neck Surg 7:323–326
6. Gao N, Li Y, Li LJ, Wen YM (2009) Clinical analysis of head and neck cancer cases in south-west China 1953–2002. J Int Med Res 37:189–197

7. Gehrking E, Gehrking I, Moubayed P (2007) Surgery of benign tumors of the parotid gland: the value of fine needle aspiration cytology. HNO 55:195–201
8. Klijanienko J, Viehl P (1997) Fine needle sampling of salivary gland lesion IV. Review of 50 cases of mucoepidermoid carcinoma with histologic correlation. Diagn Cytopathol 17:93–98
9. Viguer JM, Jimenez-Heffernan JA, Vicandi B, Lopez-Ferrer P, Limeres MA, Navarro M (2005) Cytologic diagnostic accuracy in pleomorphic adenomas of the salivary glands during 2 periods. Acta Cytol 51(1):16–20
10. Klijanienko J, Naggar AK, Viehl P (1999) Fine needle sampling in 26 carcinoma ex-pleomorphic adenomas: diagnostic pitfalls and clinical considerations. Diagn Cytopathol 21:163–166
11. Colella G, Cannavale R, Flamminto F, Foschini MP (2010) Fine needle aspiration cytology of salivary gland lesions: a systematic review. J Oral Maxillofac Surg 68:2146–2153
12. Parwani AV, Ali SZ (2003) Diagnostic accuracy and pitfalls in fine-needle aspiration interpretation of Warthin tumor. Cancer 99 (3):166–171
13. Zbären P, Schär C, Hotz MA, Loosli H (2001) Value of fine-needle aspiration cytology of parotid gland masses. Laryngoscope 111:1989–1992
14. Mihashi H, Kawahara A, Kage M, Kojiro M, Nakashima T, Umeno H, Sakamoto K, Chiziwa H (2006) Comparison of preoperative fine-needle aspiration cytology diagnosis and histopathological diagnosis of salivary gland tumors. Kurume Med J 53:23–27
15. Weinberger MS, Rosenberg WW, Meurer WT, Robbins KT (1992) Fine-needle aspiration of parotid gland lesions. Head Neck 14 (6):483–487
16. Bartels S, Talbot M, DiTomasso J, Everts EC, Andersen PE, Wax MK, Cohen JI (2000) The relative value of fine-needle aspiration and imaging in the preoperative evaluation of parotid masses. Head Neck 22:781–786
17. Lim CM, They J, Loh KS, Chao SS, Lim LHY, Tan LKS (2007) Fine needle aspiration cytology in the evaluationof parotid tumours. ANZ J Surg 77:742–744
18. Moriniere S, Perie S, St Guily JL (2007) Primary and non-primary parotidmalignancies: comparison of treatment modalities and outcomes. Eur Arch Otorhinolaryngol 264:1231–1237
19. Paris J, Facon F, Pascal T, Chrestian MA (2005) Preoperative diagnostic values of fine-needle cytology an dMRI in parotid gland tumors. Eur Arch Otorhinolaryngol 262:27–31