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Fine-needle aspiration cytology of submandibular gland lesions

Timo Atula, M.D.*, Reidar Grénman, M.D.*, Pekka Laippala, Ph.D.‡,
Pekka-Juhani Klemi, M.D.†

Abstract

The usefulness of fine-needle aspiration cytology (FNAC) in the diagnosis and treatment of submandibular gland lesions is not well known. The 210 FNACs taken from submandibular gland lesions at Turku University Central Hospital between 1984 and 1991 were reviewed. Of these FNACs, 78 samples from primary lesions were confirmed histologically. Within this subset 10 FNACs were taken from benign neoplasms, all of which were correctly classified (sensitivity 100 per cent; specificity 88 per cent). Only four of the 14 FNACs from malignant lesions were cytologically considered malignant (sensitivity 29 per cent). On the other hand, four FNACs raised a false suspicion of malignancy (specificity 6 per cent). Out of 54 FNACs from non-neoplastic lesions 43 were correct (sensitivity 80 per cent; specificity 63 per cent). There were 104 patients (123 FNACs), who had not been operated on: the follow-up of these patients shows that in this subset of FNACs there were no false malignant but probably one false benign finding (1 per cent). We conclude that FNAC can offer valuable information about the type of the submandibular gland lesion, but the decision of operative and other treatment should not be based solely on the result of FNAC.

Key words: Biopsy, needle; Submandibular gland diseases; Submandibular gland neoplasms; Cytology

Introduction

Fine-needle aspiration cytology (FNAC) is a simple method that offers additional information to that obtained by clinical examination or imaging studies. Besides a categorical diagnosis, i.e. differential diagnosis between non-neoplasia, benign neoplasm or malignant neoplasm, FNAC can often yield a type-specific diagnosis (Eneroth *et al.*, 1967; Persson and Zettergren, 1973; Lindberg and Åkerman, 1976; Qizilbash *et al.*, 1985; Nettle and Orell, 1989; Young *et al.*, 1990; Zurrida *et al.*, 1993). An operation may often be avoided when the nature of a mass can be confirmed by FNAC (Qizilbash *et al.*, 1985; Frable and Frable, 1991). FNAC is useful in determining whether the mass at the site of the salivary gland is of glandular or other origin (O'Dwyer *et al.*, 1986). Since the extent of the surgery depends on the type of the lesion, pre-operative information obtained by FNAC is useful in planning the operative treatment. FNAC is safe, quick, economical, easy to perform and causes only minimal discomfort to the patient. It has been calculated that the cost of FNAC is only 3 per cent of that of submandibular gland surgery (Frable and Frable, 1991). In addition, the cost from sick-leave after surgery adds to the cost-benefit of FNAC (Frable and Frable, 1991).

Many clinicians recommend FNAC as an initial examination of salivary gland masses (Lindberg and Åkerman, 1976; Layfield *et al.*, 1987; Frable and Frable, 1991), but still, the precise role of FNAC in the diagnosis and management of salivary gland lesions is controversial (Batsakis *et al.*, 1992). Low sensitivity in detecting malignancies has been one reason for limiting the use of FNAC (Mavec *et al.*, 1964; Eneroth *et al.*, 1967; Lindberg and Åkerman, 1976; Lau *et al.*, 1986; O'Dwyer *et al.*, 1986; Pitts *et al.*, 1992; Zurrida *et al.*, 1993). Studies of FNAC from submandibular gland lesions alone have not been published earlier. The previous studies combine the results of FNACs from submandibular and parotid gland lesions (Mavec *et al*, 1964; Eneroth and Zajicek, 1966; Eneroth *et al.*, 1967; Persson and Zettergren, 1973; Webb, 1973; Lindberg and Åkerman, 1976; Sismanis *et al.*, 1981; Qizilbash *et al*, 1985; Lau *et al.*, 1986; O'Dwyer *et al.*, 1986; Layfield *et al.*, 1987; Nettle and Orell, 1989; Young *et al.*, 1990; Frable and Frable, 1991; Pitts *et al.*, 1992) or include parotid gland lesions alone (Rodriguez*et al.*, 1989; Weinberger *et al.*, 1992; Zurrida *et al.*, 1993). The frequency of inflammatory lesions and the relative proportion of malignant neoplasms of all neoplasms is higher in the submandibular glands

From the Departments of Otorhinolaryngology*, and Pathology†, Turku University Central Hospital and the Department of Public Health/Biometry Unit‡, University of Tampere, Finland.
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than in the parotid glands. Therefore, the usefulness of FNAC in the diagnosis and management of the submandibular gland lesions is probably somewhat different than that of parotid gland lesions.

In this study, 210 FNAC were reviewed to evaluate the value of FNAC in the diagnosis of submandibular gland lesions. The FNAC findings were compared to histopathology, when available, and the follow-up of patients who were not operated on was analysed. Any delay of treatment or other disadvantages were evaluated. Multivariate analysis was performed to analyse factors for false and correct categorical diagnoses. The false-negative and false-positive cytological findings are discussed.

Materials and methods

The samples taken by the cytopathologists from submandibular gland lesions at Turku University Central Hospital between 1984 and 1991 were included in this study. The FNACs were obtained under palpation control with a 0.6 mm (23 gauge) needle and spread on slides that were stained with May–Grünwald–Giemsa. The same person who took the samples also examined the slides. The few biopsies taken by the radiologists and the clinicians were not included in this study. Altogether 210 FNACs were taken, of which 25 (12 per cent) yielded insufficient material for diagnosis.

Eighty-five FNACs were taken from 76 histologically verified primary lesions in 75 patients. Of these FNACs seven were inadequate. Two sufficient FNACs were obtained from each of eight lesions and one lesion was biopsied three times. One patient had both sides biopsied and operated on. Two FNACs were taken from recurrent tumours.

One hundred and twenty-three FNACs from 117 lesions in 104 patients were taken from lesions which were not operated on and thus lacked histological verification. Follow-up of these patients in the hospital records varied from two to nine years. A follow-up questionnaire was also sent to all living patients who had been examined in 1989 and 1990 (29 patients).

The patients comprised 86 men and 90 women with a mean age of 53.9 years (range 18–98 years). The mean age of the patients who underwent an operation (n = 75) was 52.4 years (range 18–98 years), and that of the conservatively-treated group (n = 104) 55.1 years (range 18–92 years).

If the cytopathologist was uncertain of whether the smear was benign or malignant, the FNAC was categorized as possibly malignant. Further, if there was uncertainty about whether the finding was non-neoplastic or benign neoplastic, it was categorized as benign neoplastic. If the FNAC was benign, but not specified, it was placed in the non-neoplastic category. FNACs that yielded no cells, or were reported as insufficient by the cytopathologist, were classified as inadequate.

Predictive value analysis of the histologically verified primary lesions followed published procedures (Weiss *et al.*, 1990; Weinberger *et al.*, 1992). For multivariate analysis logistic regression modelling was used (BMDP statistical software/stepwise logistic regression, Los Angeles, California, USA).

Results

Histologically verified primary lesions

The association between FNAC findings and histology of primary lesions is shown in Table I.

(i) *Benign neoplasms.* All nine benign neoplasms were pleomorphic adenomas. Ten FNACs were taken, of which eight were diagnosed as such by cytology. The additional two FNACs were taken from an atypical pleomorphic adenoma: in one smear adenoma was reported and in the other pleomorphic adenoma was considered probable.

(ii) *Malignant neoplasms.* Of the 14 FNACs taken from 12 malignant tumours only four FNACs showed signs of malignancy. Of these four FNACs two were suspicious for malignancy and two were stated as definitely malignant. These four FNACs were taken from an adenoidal cystic carcinoma, a lymphoma, and two from metastases of unknown primary tumours. None of these four lesions had been suspected to be malignant clinically. The 10 false-negative cytological findings are shown in Table II.

None of the patients with lymphomas were known to have the disease previously, and only one of the lymphoma patients had more than one lesion.

(iii) *Non-neoplastic lesions.* Forty-three (80 per cent) FNACs out of 54 taken from 47 lesions were correctly reported as non-neoplastic.

A benign adenoma was suspected in seven (13 per cent) cytological samples, but none of these samples were considered as definitely neoplastic. Histologically, two of these lesions were benign lympho-

TABLE I

ASSOCIATION BETWEEN CYTOLOGICAL FINDINGS OF FINE-NEEDLE ASPIRATION CYTOLOGY (FNAC) AND HISTOLOGICAL DIAGNOSES FROM PRIMARY SUBMANDIBULAR GLAND LESIONS

	Histology			
Cytology	Non-neoplastic	Benign neoplastic	Malignant	Total no. of FNACs
Non-neoplastic	43	–	9	52
Benign neoplastic	7	10	1	18
Possibly malignant	3	–	2	5
Malignant	1	–	2	3
Inadequate	6	1	–	7
Total	60	11	14	85

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TABLE II
FINE-NEEDLE ASPIRATION CYTOLOGY (FNAC) FROM PRIMARY SUBMANDIBULAR GLAND LESIONS (N = 78) STATED FALSELY AS BENIGN (N = 10)

	Histology				
Cytology	Lymphoma	Adenoid cystic carcinoma	Mucoepidermoid carcinoma	Squamous cell carcinoma	Total no. of FNACs
Normal tissue	1	1	1	1	4
Non-specific inflammation	2	1	–	–	3
Granulomatous lesion	2	–	–	–	2
Pleomorphic adenoma	–	1	–	–	1
Total	5	3	1	1	10

epithelial lesions and the rest were inflammatory lesions.

Malignancy was suspected in three FNACs from inflammatory lesions. Further, one FNAC was stated falsely as definitely malignant in a patient, who had had acinic cell carcinoma in the parotid gland treated by surgery and radiotherapy two years previously. The same kind of tumour was reported by cytology, but histology showed only inflammation.

Recurrent tumours

Correct type-specific cytological findings were obtained from one pleomorphic adenoma and one adenoid cystic carcinoma.

Statistical analysis

The determinant for the predictive value of FNAC as a method with which to identify non-neoplastic, benign neoplastic and malignant submandibular gland tumours is shown in Table III (Weiss *et al.*, 1990; Weinberger *et al.*, 1992). Multivariate analysis was performed to explain correct or false categorical diagnoses (non-neoplastic – benign neoplastic – malignant). The following variables were considered: size and history of the lesion, age and sex of the patient, year of sampling, prior FNACs, prior surgery at the same site, previous or current malignancy in the head and neck region and sample/interpretation of the sample. None of these variables were significantly associated with correct or false categorical diagnoses.

TABLE III
PREDICTIVE VALUES OF FINE NEEDLE ASPIRATION CYTOLOGY OF THE SUBMANDIBULAR GLAND LESIONS (N = 78). POSSIBLY MALIGNANT FINDINGS WERE CLASSIFIED AS MALIGNANT

	Non-neoplasia *versus* others (%)	Benign neoplasia *versus* others (%)	Malignant *versus* others (%)
Accuracy	74	90	82
Sensitivity	80	100	29
Specificity	63	88	94
False-negative rate	20	0	71
False-positive rate	38	12	6
Positive predictive value	83	56	50
Negative predictive value	58	100	86

The cytological statement of pleomorphic adenoma was significantly more reliable than statements of other types of benign neoplasms (Fisher's Exact: $p = 0.0029$).

FNAC of the lesions not verified histologically

The distribution of the cytological findings of the 123 FNACs not verified histologically is shown in Table IV. Of these samples 18 were reported as inadequate. Benign cytological findings were obtained in 103 FNACs, of which one FNAC may have been a false-negative: a patient with gingival carcinoma had a mass, which was reported as a benign adenoma by cytology. After radiotherapy the mass disappeared and surgery was not performed due to the general condition of the patient. Later on, the patient died with recurrent cancer. In the follow-up of at least two years, no other patients, who had a benign cytological finding, developed any disease related to the submandibular gland mass or died of disease related to the submandibular gland lesion.

FNAC was stated as benign neoplastic in six other lesions: four of these were not operated on due to the poor general condition of the patients; one lesion showed a lipoma and was unchanged after seven-year follow-up; one patient refused an operation.

Signs of malignancy were reported in two FNACs. These patients had had carcinomas in the head and neck region previously. The recurrent carcinomas were confirmed by FNAC, and, later, the patients died of their cancer.

All 29 patients who received the questionnaire responded. The lesion had not grown in any of the patients. The patient, who refused surgery initially, had been treated surgically elsewhere. The histopathological analysis at the other hospital confirmed pleomorphic adenoma reported in the cytological examination.

Complications

A small haematoma after the biopsy was reported in two patients (1 per cent).

The FNAC that was falsely reported as definitely malignant led to the decision to perform an unnecessary functional neck dissection, although no

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TABLE IV
FINE-NEEDLE ASPIRATION CYTOLOGY (FNAC) FINDINGS FROM SUBMANDIBULAR GLAND LESIONS NOT VERIFIED HISTOLOGICALLY (N = 123)

	FNAC finding									
Palpation finding	Inadequate sample	Normal parotid gland tissue	Inflam-mation	Granulo-matous lesion	Cyst	Other benign non-neoplastic lesions	Benign neoplasm	Possibly malignant	Malignant	Total no. of FNACs
Diffuse lesion	12	21	12	–	1	19	1	–	–	66
Tumour	6	15	11	–	2	11	6	1	–	52
Type of lesion not specified	–	–	1	2	–	1	–	–	1	5
Total	18	36	24	2	3	31	7	1	1	123

definitive tumour was any longer palpable at the time of the operation.

It is possible that there was a delay in the treatment of two patients partly because of the false-negative cytological findings. The first patient had had a hard lesion (size 1.5 cm) 18 months before the initial FNAC, which showed inflammation. The second FNAC one year later was suspicious for malignancy and the operation confirmed lymphoma. The second patient had had hypoglossus paresis for one year at the time of the initial FNAC from a slightly palpable lesion. The initial FNAC showed normal tissue morphology. The second FNAC from the slightly enlarged lesion two years later showed inflammation, but histology revealed an adenoid cystic carcinoma.

Discussion

The accuracy of FNAC for benign neoplasms was 90 per cent in this study (Table III). All benign neoplasms were pleomorphic adenomas, all of which were correctly detected by FNAC. Of the FNACs reported as probably or definitely pleomorphic adenomas (n = 10) one lesion was an adenoid cystic carcinoma, but all the others were correct. Other studies also report high sensitivity (around 90 per cent) for the diagnosis of pleomorphic adenomas by FNAC (Eneroth and Zajicek, 1966; Eneroth *et al.*, 1967; Persson and Zettergren, 1973; Lindberg and Åkerman, 1976; Lau *et al.*, 1986; O'Dwyer *et al.*, 1986; Nettle and Orell, 1989; Pitts *et al.*, 1992). Furthermore, our results support other series, which show that the cytological finding of a pleomorphic adenoma is correct in about 90 per cent of the samples (Mavec *et al.*, 1964; Eneroth *et al.*, 1967; Qizilbash *et al.*, 1985; Layfield *et al.*, 1987; Orell and Nettle, 1988; Nettle and Orell, 1989; Rodriguez *et al.*, 1989; Pitts *et al.*, 1992).

The accuracy in detecting malignant tumours was 82 per cent. The low sensitivity for malignancy (28 per cent) remains a problem in this study as well as in many other series from salivary gland tumours (Mavec *et al.*, 1964; Eneroth *et al.*, 1967; Lindberg and Åkerman, 1976; Lau *et al.*, 1986; O'Dwyer *et al.*, 1986; Cross *et al.*, 1990; Pitts *et al.*, 1992; Weinberger *et al.*, 1992; Zurrida *et al*, 1993). The sensitivity in detecting malignant tumours in large studies from salivary glands is often less than 70 per cent (Mavec *et al.*, 1964; Eneroth *et al.*, 1967; Lau *et al.*, 1986; Pitts *et al.*, 1992; Zurrida *et al.*, 1993), but in a number of studies it exceeds 85 per cent (Persson and Zettergren, 1973; Webb, 1973; Sismanis *et al.*, 1981; Qizilbash *et al*, 1985; Layfield *et al.*, 1987). The results are often difficult to compare between different studies (see Layfield *et al.*, 1987). We included the FNACs that show normal salivary gland tissue in the statistical analysis and did not classify them as inadequate, which may partly explain our lower sensitivity for malignant tumours in comparison to some other studies.

On the other hand, false-positive cytological findings are rare: in this study the rate was 6 per cent if possibly malignant lesions were included and 2 per cent if only definitely malignant lesions were considered. Our results are consistent with other studies, which show that the false-positive rates for malignancy range from 0 per cent (Qizilbash *et al.*, 1985; Lau *et al.*, 1986; Zurrida *et al*, 1993) to 6 per cent (O'Dwyer *et al.*, 1986; Weinberger *et al.*, 1992).

The accuracy with which neoplasms were separated from non-neoplastic lesions was 74 per cent. The corresponding rate in other studies varied from 24 per cent (Pitts *et al.*, 1992) to 100 per cent (Webb, 1973; Zurrida *et al.*, 1993). Inflammation may lead to erroneous suspicion of malignancy (Layfield *et al.*, 1987; Young, 1989), which also occurred in the four false-positive FNACs in our study.

Of the 10 false-negative cytological findings, four FNACs showed only normal salivary gland tissue (Table II). It is likely that in these cases the needle had not hit the tumour. It is important that the clinician does not rely on the cytological findings of normal tissue in a case presenting with a definite tumour.

Of the histologically verified samples 25 FNACs showed inflammation including five with granulomatous findings. Five of these were malignant on histology, and four of these turned out to be lymphomas (Table II). Others have also reported that lymphoma is difficult to diagnose from FNAC (Lindberg and Åkerman, 1976; Qizilbash *et al.*, 1985; O'Dwyer *et al.*, 1986; Layfield *et al.*, 1987; Layfield and Glasgow, 1991; Zurrida *et al.*, 1993). Therefore, it is important that every mass that shows signs of inflammation must be followed up, and if the mass

does not disappear, repeated FNAC or surgery should be carried out.

In other studies many errors have been reported to be caused by the cytological finding of cystic fluid only (Mavec *et al.*, 1964; Eneroth *et al.*, 1967; Persson and Zettergren, 1973; Lindberg and Åkerman, 1976; Cohen *et al.*, 1986; O'Dwyer *et al.*, 1986; Frable and Frable, 1991; Pitts *et al.*, 1992; Zurrida *et al.*, 1993). In this study, all the FNACs that showed cystic fluid only were correct, but only five samples were confirmed by histology.

In addition to the histologically verified lesions, 123 FNAC were performed from lesions that were confirmed by clinical course only (Table IV). The follow-up of the conservatively treated patients (n = 104) in our study indicates that surgery may sometimes be avoided. It is also noteworthy, that although the cytological finding of inflammation caused many errors in the histologically verified lesions, an additional 24 FNACs showing non-specific inflammation were taken from lesions, that did not later need operative treatment. It has been estimated that 30 per cent of the operations may be avoided when the nature of the lesion can be confirmed by FNAC (Qizilbash *et al.*, 1985).

In this study, 12 per cent of the samples were reported inadequate. We have noted, that the corresponding percentage in parotid gland lesions is 2 per cent (Atula *et al.*, 1995). These numbers, as well as the low sensitivity for malignant tumours, indicate that it is more difficult to get an adequate sample from a submandibular gland lesion than from a parotid gland lesion.

FNAC causes no major complications. Minor haematomas occur occasionally. In our patients no infections were reported after FNAC. A probable delay in the treatment in two patients was due to false-negative findings. This could have been avoided if the limitations of the method had been realized. In addition, the FNAC that was falsely stated as definitely malignant may have led to an unnecessary large operation. Other possible, but rare, complications of FNAC may include tumour necrosis (Kern, 1988; Batsakis *et al.*, 1992) and seeding of tumour cells which may take place in perhaps 0.005 per cent of the samples (Smith, 1984).

In order to improve the accuracy of FNAC especially in lesions situated deep in the neck ultrasound-guided biopsies have been used (Baatenburg de Jong *et al.*, 1991). In this study we have evaluated the results of FNACs obtained under palpation control, since that is the method commonly used by many clinicians.

Conclusions

Fine-needle aspiration cytology (FNAC) offers valuable information not obtained by any other means. However, this study shows that the clinician should be careful in interpreting the cytological findings from submandibular gland lesions. The clinician should not rely solely on the results of FNAC, but the cytological finding must be in agreement with the clinical evaluation. If the FNAC shows benign findings in a lesion that is not to be operated on, follow-up is mandatory. FNAC is highly accurate in detecting pleomorphic adenomas but the sensitivity in detecting malignant tumours is low. In comparison with studies of parotid gland lesions, the false-positive rate was shown to be about the same, but the sensitivity in detecting malignant tumours was lower.

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Address for correspondence:
Dr Timo Atula,
Department of Otorhinolaryngology,
University of Turku,
Fin-20520,
Turku,
Finland.

Fax: +358-21-2613550