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MAIN ARTICLE

Routine non-thyroid head and neck cytology in a large UK centre: clinical utility and pitfalls

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Abstract

Objective: This study aimed to examine the performance of head and neck cytology at Nottingham University Hospitals between 2009 and 2010.

Methods: Cases were extracted from the Winpath pathology reporting system and correlations were investigated between results and the histological and clinical outcomes. Specimen adequacy and the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of the cytology tests were calculated.

Results: In all, 19.7 per cent of aspirates were judged to be inadequate. The absolute and relative sensitivities of head and neck cytology were 87.0 per cent and 89.0 per cent, respectively, and the absolute and relative specificities were 99.0 per cent and 97.0 per cent, respectively. The positive predictive values were 99.0 per cent and 96.0 per cent and the negative predictive values were 92.0 per cent and 92.0 per cent for a diagnostic accuracy of 94.5 per cent and 93.0 per cent. The performance was consistent with previous reports and superior to that of a recent UK series. The high rate of inadequate samples is, however, a concern.

Conclusion: Head and neck cytology is a robust technique at our institution, although there are certain problem areas. There is room for improvement in the technical quality of fine needle aspiration.

Key words: Cytology; Head and Neck Neoplasms; Sensitivity and Specificity: Salivary Glands; Lymph Nodes

Introduction

Cytology forms an important part of the diagnostic process for a variety of different head and neck pathologies. This includes investigating salivary masses, cervical lymphadenopathy and lumps in the neck and obtaining a tissue diagnosis for suspected metastatic cancers, especially lung carcinomas.

The reported accuracy of cytological analysis varies by the disease context: it is best for diagnosing metastatic cancer and worst for diagnosing non-Hodgkin's lymphoma.[1] This is particularly true when modern diagnostic techniques (e.g. immunophenotyping, preferably by flow cytometry) are not routinely performed.[2]

The usefulness of the test depends not only on the laboratory performance but also on the sample quality. Therefore, this study was primarily performed to compare our own diagnostic accuracy with that of other centres and reported studies. Another aim was to identify areas of good practice and areas requiring attention. In contrast to previous studies, this one reports not only restricted (adequate samples only) but also overall (all submitted samples) sensitivity analyses. This provides a worse figure for overall sensitivity but a truer reflection of the test performance in routine practice.

Materials and methods

The study was approved by and registered with the Nottingham University Hospitals audit authority.

The Nottingham University Hospitals computer system, Winpath, was searched for all cases registered under the specimen type codes 'fine needle aspiration' (FNA), 'lymph node FNA', 'neck FNA', 'parotid gland FNA', 'submandibular gland FNA' and 'submental FNA' between 1 January 2008 and 31 December 2009. All cases not of head and neck origin were excluded from further analysis, as were superficial skin lumps. Selected cases therefore involved salivary gland, cervical and supraclavicular lymph node, and neck lump aspirates and a few miscellaneous facial aspirates. Each case was interrogated on the Winpath system for the origin (salivary gland, lymph node or lump in neck not otherwise specified), cytological diagnosis, cytological category, histological diagnosis (when the sample area had subsequently been subjected to histological analysis), histological category and clinicopathological diagnosis (when a definite histological diagnosis had been made). Where the area had not been histologically analysed, the hospital information system (Nottingham Acute Hospital Partnership Information and Communications

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Technology Services) was reviewed to determine the eventual diagnosis based on clinical, radiological and cytological information and clinical follow up. In some cases, sufficient follow-up information was unavailable, and this was recorded.

All specific cytological, histological and clinicopathological diagnoses were classified into 1 of the 24 diagnostic groups shown in Table I. Cytological, histological and clinicopathological categories are shown in Table II. Haematological cases were classified into groups 4, 5, 10, 11, 20 and 23.

The database was analysed using IBM SPSS Statistics software version 17.0 (Chicago, Illinois, USA). Diagnostic accuracy was determined using an online sensitivity and specificity calculator.[3]

The following definitions were used. Absolute diagnostic accuracy was analysed by considering only category 5 as positive. It was further analysed in two ways: overall, by considering all other categories as negative (including 1 and 4); or restricted, by considering only category 2 as negative. Relative diagnostic accuracy was analysed by considering both categories 4 and 5 as positive. Similarly, it was further analysed as overall or restricted (i.e. with or without inadequate cytology). Overall diagnostic accuracy was determined by the following calculation: (true negatives plus true positives) divided by (true negatives plus true positives plus false negatives plus false positives). Suspicious cytology findings were also analysed separately to ascertain the significance of a suspicious result in our laboratory. This was done by including only category 4 as positive and category 2 (i.e. benign) as negative.

Inadequate samples are excluded from specificity and sensitivity analyses in many reported series, and only the restricted figures are reported. While this can be justified as inadequate samples do not reflect the performance of cytology interpretation, it is also useful to know the overall performance of the test by including all of its components. For this reason, both overall and restricted figures are included in the analysis.

TABLE I
DIAGNOSTIC GROUPS

Group	Diagnosis
1	Inadequate sample
2	Benign, not otherwise specified
3	Cyst, not otherwise specified
4	Reactive node
5	Node, uncertain whether benign or malignant
6	Inflammatory tissue
7	Adenocarcinoma
8	Carcinoma, not otherwise specified
9	Squamous carcinoma
10	Lymphoma
11	Suspicious for lymphoma
12	Suspicious for squamous carcinoma
13	Suspicious, other
14	Branchial cyst
15	Atypical cytology
16	Papillary thyroid carcinoma
17	Granulomatous inflammation
18	Lipoma
19	Melanoma
20	Mature lymphocytes, non-malignant cells
21	Pleomorphic adenoma
22	Warthin's tumour
23	Radiologically or clinically benign node
24	Benign vascular lesion

TABLE II
CYTOLOGICAL, HISTOLOGICAL AND CLINICOPATHOLOGICAL CATEGORIES

Category	Description
1	Inadequate sample
2	Benign (groups 2–4, 6, 14, 17, 18, 20–24)
3	Atypical (groups 5, 15)
4	Suspicious for malignancy (groups 11–13)
5	Malignant (groups 7–10, 16, 19)

Results

Whole series

In all, 704 cases were subjected to cytological analysis and the diagnosis was confirmed histologically in 372 (52.8 per cent). A total of 659 patients (93.5 per cent) received a clinicopathological diagnosis, leaving 45 cases (6.4 per cent) with missing outcome data.

Diagnostic frequency

A total of 139 FNA samples (19.7 per cent) were deemed inadequate or insufficient for diagnosis (category 1). Of the remainder, 167 (23.7 per cent) were classified as malignant (category 5) and 352 (50.0 per cent) as benign (category 2), with 6.6 per cent in intermediate categories.

Diagnostic accuracy based on clinicopathological outcome

Of the 704 cases, a clinicopathological outcome was recorded for 659: the outcome was defined histologically for 372 and by clinical and radiological follow up for the remainder. Forty-five patients had no histologically defined outcome or adequate follow up recorded in the Nottingham Acute Hospital Partnership Information and Communications Technology Services ('NOTIS'). Table III compares the cytology category with the final clinicopathological category, and Table IV shows the

TABLE III
WHOLE SERIES: CROSS-TABULATION

Cytology category	Clinicopathological category (*n*)					
	1	2	3	4	5	Total
1	1	87	0	1	33	122
2	0	272	2	0	24	298
3	0	17	1	0	12	30
4	0	8	1	1	35	45
5	0	1	0	0	163	164
Total	1	385	4	2	267	659

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TABLE IV
WHOLE SERIES: SENSITIVITY AND SPECIFICITY ANALYSIS

Variable	Absolute (%)		Relative (%)		Suspicious cytology (%)*
	Overall	Restricted	Overall	Restricted	
Sensitivity	61.0	87.0	74.0	89.0	60.0
Specificity	99.7	99.0	98.0	97.0	97.0
PPV	99.0	99.0	96.0	96.0	82.0
NPV	79.0	92.0	85.0	92.0	92.0

*Category 4 versus category 2. PPV = positive predictive value; NPV = negative predictive value

TABLE V
HAEMATOLOGICAL CATEGORY: CROSS-TABULATION

Cytological category	Haematological clinicopathological category (*n*)					
	1	2	3	4	5	Total
1	1	38	0	0	4	43
2	0	106	0	0	12	118
3	0	8	0	0	5	13
4	0	2	0	1	11	14
5	0	1	0	0	10	11
Total	1	385	0	1	42	199

respective sensitivity and specificity analysis. The absolute diagnostic accuracy (restricted) was 94.5 per cent and the relative diagnostic accuracy (restricted) was 93.0 per cent.

Haematological disease

Obtaining a cytological diagnosis of lymphoma poses particular problems, especially where additional techniques such as flow cytometry are not used as an adjunct. This is the case at our institution. We therefore analysed these cases separately by only examining lymph node aspirates for which benign or haematological disease diagnosis was based on cytological and/or histological analysis and/or clinical follow up. In this way, 199 cases were identified for inclusion.

Table V shows the cytology and final clinicopathological haematological category cross-tabulation and Table VI shows the respective sensitivity and specificity analysis. The absolute diagnostic accuracy (restricted) was 90.0 per cent and the relative diagnostic accuracy (restricted) was 89.0 per cent.

Salivary gland

In all, 193 patents had salivary gland aspirates taken. Of these, 26 had inadequate histological or clinical follow up, leaving 167 included in the analysis.

Table VII shows the cytology and final clinicopathological salivary category cross-tabulation and Table VIII shows the respective sensitivity and specificity analysis. The absolute diagnostic accuracy (restricted) was 97.5 per cent and the relative diagnostic accuracy (restricted) was 95.0 per cent.

Branchial cyst diagnosis

Of the 22 branchial cysts identified cytologically, the diagnosis was confirmed for 17 and a further 3 were later identified as unspecified cysts. One diagnosis of cytology suspicious for squamous cell carcinoma (SCC) and another of atypical cytology were later identified as branchial cysts. Conversely, 2 out of 19 cases cytologically diagnosed as branchial cysts were later identified as malignant: 1 lymphoma and 1 SCC.

Squamous cell carcinoma diagnosis

Of 37 cases cytologically diagnosed as SCC, 35 were later confirmed, while the remaining 2 were identified as other carcinoma types. Of the 66 SCC cases diagnosed histologically after adequate smears, 35 had been cytologically diagnosed as SCCs, 10 as unspecified carcinomas, 1 as an adenocarcinoma and a further 11 as suspicious. Five cases had negative cytology findings.

Metastatic papillary thyroid carcinoma diagnosis

Of seven papillary carcinomas, only two were recognised as such by cytology and a further two were cytologically diagnosed as other malignancies.

TABLE VI
HAEMATOLOGICAL CATEGORY: SENSITIVITY AND SPECIFICITY ANALYSIS

Variable	Absolute (%)		Relative (%)		Suspicious cytology (%)*
	Overall	Restricted	Overall	Restricted	
Sensitivity	24.0	45.0	51.0	64.0	48.0
Specificity	99.0	99.0	98.0	97.0	98.0
PPV	91.0	91.0	88.0	87.0	85.0
NPV	83.0	90.0	88.0	90.0	89.0

*Category 4 versus category 2. PPV = positive predictive value; NPV = negative predictive value

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TABLE VII
SALIVARY CATEGORY: CROSS-TABULATION

Cytological category	Salivary clinicopathological category (*n*)					
	1	2	3	4	5	Total
1	0	21	0	1	2	24
2	0	108	0	0	3	111
3	0	7	0	0	3	10
4	0	3	1	0	5	9
5	0	0	0	0	13	13
Total	0	139	1	1	26	167

Discussion

We report the comprehensive analysis of a large series of FNA samples from the head and neck region.

Diagnostic frequency

The most prominent result is the large number of inadequate samples: 139 (almost 20 per cent). A significant proportion of these (24.0 per cent) were identified as malignant by histology or repeated FNA cytology. This represents an area where improved performance is required. Although reported inadequate sample rates in many series are above 10.0 per cent, they do not usually exceed 15.0 per cent. Exceptions were the Sussex and Leeds audits (UK), which reported very poor adequacy rates.[4,5] A recent UK study from Berkshire designed to assess the value of on-site evaluation also showed a non-diagnostic rate of 22 per cent.[6] This audit did not examine the relationship between the origin of inadequate aspirates and specific users or sampling method (e.g. ultrasound guided versus free-hand), nor whether the rate might differ according to pathologist interpretation. In the Leeds study that yielded a 28 per cent inadequate sample rate, ultrasound-guided aspirates were not of better quality than those obtained without imaging. However, an inadequate sample rate is a significant concern, partly because of the wasted effort and time. Another potential consequence of receiving poor quality material is that pathologists may be tempted to overinterpret smears which are paucicellular, too thick or poorly stained. Thus, technically inadequate smears might, in some instances, contribute to significant diagnostic errors. In some countries, it is normal for pathologists to perform FNA, and this is suggested to provide optimal material.[7] However, this does not usually occur in the UK and FNA does not form part of the Pathology curriculum. Other studies have shown that on-site assessment of sample adequacy also improves sample quality.[8] This is feasible at our institution but would require dedicated resourcing because it has significant manpower implications. Of interest, the Berkshire study did not show a large improvement in adequacy with repeated FNA after on-site assessment, and concluded that it would not merit the additional cost.[6] It is generally believed, with some supporting evidence, that whichever type of practitioner performs the FNA, a dedicated structured training programme in the use of this technique is essential to obtain optimal quality.[9] This is lacking in UK training programmes and probably explains the high inadequate sample rates reported in series from this country.

Diagnostic accuracy: whole series

Based on clinicopathological outcome, including inadequate smears, the absolute sensitivity was 61.0 per cent and specificity was 99.7 per cent. Most reported series exclude inadequate samples from diagnostic accuracy calculations.[2,4,5,10–12] By excluding inadequate samples, the sensitivity rose to 87.0 per cent and the specificity was 99.0 per cent, with just a single false positive; the overall diagnostic accuracy was 94.5 per cent. This yielded a positive predictive value of 99.0 per cent and a negative predictive value of 92.0 per cent. These figures compare very well with reported values for diagnostic accuracy, and are better than those of recent audits from Sussex and Leeds, even excluding the thyroid cytology component of those audits.[2,4,5,10]

Calculations of relative accuracy include cases diagnosed as suspicious for malignancy. When these were included, the test specificity fell to 97.0 per cent, with nine false positives, while the sensitivity increased to 89.0 per cent (excluding inadequate samples).

Of the 45 cases reported as suspicious, 35 were later identified as malignant, and a further 2 showed atypical or suspicious histology (1 was an atypical lymphoid hyperplasia and bone marrow biopsy identified the other as a probable follicular lymphoma) and 8 were unequivocally benign. This yielded a sensitivity of 60.0 per cent, a specificity of 97.0 per cent and a positive predictive value of 82.0 per cent.

TABLE VIII
SALIVARY CATEGORY: SENSITIVITY AND SPECIFICITY ANALYSIS

Variable	Absolute (%)		Relative (%)		Suspicious cytology (%)*
	Overall	Restricted	Overall	Restricted	
Sensitivity	50.0	81.0	69.0	86.0	63.0
Specificity	100	100	97.0	96.0	97.0
PPV	100	100	82.0	82.0	82.0
NPV	92.0	97.0	94.0	97.0	94.0

*Category 4 versus category 2. PPV = positive predictive value; NPV = negative predictive value

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Of the cases diagnosed as atypical, 12 out of 30 (40.0 per cent) were later shown to be malignant, indicating that this diagnosis always warrants further investigation.

One problem with calculating the values for suspicious cytology is that different pathologists adopt different usages of the term 'suspicious'. For pancreatic cytology, pathologists at our institution routinely use a numerical scoring system; however, a similar system is not used for neck FNA samples, except for those of the thyroid. Consequently, one pathologist may restrict use the term 'suspicious' to cases which are highly likely to be malignant, whereas another may use this term for any case showing atypical cells for which the diagnosis is uncertain. It may therefore be beneficial to introduce a cytology scoring system for head and neck pathology, or at least to agree to more precise definitions. Such an approach has been successfully introduced at a national UK level for thyroid cytology and might be beneficial in other areas.[13]

Cytology in haematopathology

Cytological analysis is known to be problematic for lymph node pathology and most reported series have shown that sensitivity for lymphoma diagnosis is lower than for other pathologies.[4,5,12] This series is no exception: the absolute sensitivity (including inadequate samples) was only 24.0 per cent. After restricting the analysis to adequate samples, the absolute sensitivity was 45.0 per cent and the relative (including samples with suspicious cytology) was 64.0 per cent. Thus, of the 42 lymphomas, 4 had inadequate samples and 10 were diagnosed as malignant, 11 as suspicious, 5 as atypical and 12 as benign. However, the vast majority of reactive lymph nodes were correctly diagnosed and the negative predictive value was good at 90.0 per cent; the positive predictive value was also high, at 91.0 per cent. There was one false positive, although this was actually not a misdiagnosis of lymphoma but rather a diagnosis of metastatic carcinoma in a patient with known colorectal cancer. In this case, subsequent biopsy showed a reactive node and clinical follow up indicated it to be benign. Other studies have shown a highly variable degree of accuracy for lymphoma diagnosis. In some institutions, lymphoid cytology is combined with flow cytometry or routine immunohistochemistry. This generally yields a more accurate diagnosis (quoted sensitivities of more than 80.0 per cent) but it does use significantly more resources.[2,11] In our false negative cases, cytology was usually rapidly followed by lymph node biopsy because of suspicious clinical and radiological results, and little time was lost. In these patients, lymph node biopsy would be needed even after a confident cytological diagnosis of lymphoma; there therefore seems little to gain by investing a large amount of time and resources into developing special cytological techniques. However, it should be emphasised that at our institution cytology is not a robust tool for lymphoma diagnosis; specifically, a negative finding does not rule out Hodgkin's or low-grade non-Hodgkin's lymphoma. Conversely, a definite or suspected lymphoma diagnosis is highly predictive of a histological diagnosis of lymphoma. Close correlation between clinicopathological and radiological findings is always required.

Salivary gland pathology

The absolute sensitivity for diagnosing salivary gland cancer was 50.0 per cent for the whole series and 81.0 per cent after excluding inadequate samples and restricting the analysis to benign and malignant diagnoses. The specificity and positive predictive value was 100 per cent for a diagnostic accuracy of 97.5 per cent. The relative sensitivity (including suspected diagnoses) was 86.0 per cent and the specificity was 96.0 per cent, with a positive predictive value of 82.0 per cent and negative predictive value of 97.0 per cent. These values are within the reported range, which is generally quoted as a sensitivity of about 80.0 per cent and specificity of above 90.0 per cent.[14,15] Of the 26 malignant cases assessed histologically, benign cytology findings were obtained for 3. One was an adenoid cystic carcinoma misdiagnosed as a pleomorphic adenoma and another was a mucoepidermoid initially assessed as a benign epithelial cyst. The third was an oncocytic carcinoma which showed few oncocytes in a scanty smear that was borderline for adequacy; however, findings were consistent with a clinical diagnosis of Warthin's tumour. Of eight cases with atypical cytology, three proved to be malignant, thus showing the diagnostic importance of this category. The three cases diagnosed as suspicious with benign histology findings included a myofibroblastic proliferation which cytological analysis revealed to include atypical spindle cells, a Warthin's tumour with atypical squamoid cells (a known diagnostic pitfall[16]) and an unusual case with cytology findings of highly atypical cells for which neck dissection yielded completely negative findings.

Regarding the specific diagnosis of salivary tumour, there were only sufficient numbers of pleomorphic adenomas and Warthin's tumours for assessment. Excluding inadequate smears, both were diagnosed with a high degree of accuracy, with 31 out of 34 pleomorphic adenomas and 17 out of 24 Warthin's being correctly diagnosed, with only a single malignant to benign diagnostic reversal, as noted above. These findings are consistent with previous reports.[12,17]

Diagnosis of branchial cysts and squamous carcinoma

Branchial cysts and squamous carcinoma can sometimes be mistaken for each other because both can feature well-differentiated squamous cells. This audit showed good diagnostic accuracy for each diagnosis by FNA cytology. Nevertheless, one branchial cyst was diagnosed as suspicious for SCC and, conversely, two cases diagnosed as branchial cysts were malignant: one a SCC and one a lymphoma. There was also very

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good specificity for SCC diagnosis, with 98.8 per cent correct for tumour type. However, sensitivity for tumour type was less good, with 10 out of 66 diagnosed as unspecified carcinomas, 11 as suspicious and a further 5 as negative. This is to be expected because it is likely that only better differentiated tumours would be correctly typed by FNA cytology.

- **Fine needle aspiration cytology is widely used in head and neck lesion diagnosis**
- **Inadequate sample rates vary widely and may be high**
- **The diagnostic accuracy of fine needle aspiration cytology was high**
- **Training of aspirators in the UK needs to be improved**
- **Clinicians should be aware of the problems associated with cytology, in particular the difficulty of excluding lymphoma**

Diagnosis of unsuspected metastatic papillary thyroid carcinoma

Cytological diagnosis of metastatic papillary thyroid carcinoma was particularly problematic in this audit. Of the seven papillary carcinomas, only two were correctly identified; a further two were diagnosed as other malignancies and three as benign cysts. Cystic change in papillary carcinoma is well recognised and, as always, if clinical and radiological analyses indicate that a lesion is partly solid and partly cystic then a cytological diagnosis of a benign cyst should not be accepted without further sampling.

Conclusion

This audit showed that, in general, head and neck cytology provides a useful, if imperfect, contribution to diagnosis at our institution. Known weaknesses, especially regarding sensitivity for lymphoma diagnosis, were confirmed and some classical diagnostic pitfalls in salivary and branchial cyst pathology were recognised. In general, the diagnostic accuracy compares well with previous reports; nevertheless, this may be further improved by reviewing all malignant and suspicious diagnoses by a multidisciplinary team, including discussion of the clinical and radiological context, in the same way that histology findings are reviewed. In addition, similar to previously published large UK audits, there was a relatively high inadequate sample rate. While this study was not designed to investigate the reasons for inadequate cytology, it is accepted that a good performance of FNA cytology requires a dedicated training programme to obtain fewer but more highly skilled aspirators. Unfortunately, this is a neglected area in UK medical training.

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