

Thyroid FNAC cytology: can we do it better?

D. N. Poller*, E. B. Stelow[†] and C. Yiangou[‡]

*Department of Pathology, Queen Alexandra Hospital, Portsmouth, UK, [†]Department of Pathology and Laboratory Medicine, University of Virginia, Charlottesville, VA, USA and [‡]Department of Surgery, Queen Alexandra Hospital, Portsmouth, UK

Accepted for publication 15 June 2007

D. N. Poller, E. B. Stelow and C. Yiangou

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This article reviews recent developments in thyroid fine needle aspiration cytology (FNAC). While thyroid nodules are common, carcinoma is comparatively rare. Although histological assessment is used in most studies as the benchmark, the differential diagnosis on cytology or histology is not always reproducible. The literature shows wide variations in criteria for inadequate thyroid FNAC and study inclusion or exclusion criteria. In-clinic assessment of specimen adequacy and in-clinic reporting of thyroid FNAC has become popular although the costs and resource implications of in-clinic thyroid FNAC assessment and reporting are substantial. Many centres continue to use conventional techniques although liquid-based cytology and ultrasound-guided FNAC are gaining in popularity. Standardized categorical systems for FNAC reporting can make results easier to understand for clinicians and give clear indications for therapeutic action. Multidisciplinary case review is also essential, especially when there is diagnostic uncertainty. While currently of limited use, molecular pathology testing holds out some promise for the future.

Keywords: thyroid gland, cytology, cytodagnosis, FNAC, classification systems, inadequate samples

Thyroid fine needle aspiration cytology (FNAC) is over 50 years old¹ and is the principal method of preoperative diagnosis in both children and adults. It has been shown to be superior to clinical, radionuclide or thyroid ultrasound assessment alone. FNAC requires careful aspiration technique and interpretation of the cytological findings. Most practitioners rely on FNAC alone, especially for the first attempt at diagnosis. Core biopsy histological assessment of the thyroid is described in the literature² and core biopsy cytological assessment of the thyroid is used in some centres.³ Some cytologists take their own aspirates^{4,5}, others do not. Although the procedure has changed little with time, there have been a number of important recent developments. This review addresses some of these issues and trends, emphasizing ways of improving the overall diagnostic process and the use of clinical resources.

Thyroid disease

Thyroid nodules are very frequent, with a number of studies showing an annual incidence rate of 4–8%.⁶ Autopsy and ultrasound data suggest that the prevalence rate for thyroid nodules in clinically normal individuals is around 50%.⁷ Three to sixteen per cent of patients who undergo thyroidectomy for benign disease are found to have incidental malignancies, mostly small papillary carcinomas less than 10 mm in size, the majority of which are of little significance.⁸ Despite the high prevalence of thyroid nodules and incidental malignancies, the prevalence of clinically overt thyroid carcinoma is much lower. In 2002, in the UK, the crude incidence of thyroid cancer was 2.6 cases per 100 000 patient years⁹ and in 2004 the crude thyroid cancer mortality was 0.5 cases per 100 000 patient years.¹⁰ Thus most thyroid nodules are benign and most thyroid cancers are not lethal. While thyroid FNAC leads to earlier detection, sampling and treatment of differentiated thyroid cancers, it is not possible to predict which differentiated thyroid cancers will behave aggressively and there is no conclusive evidence to show that the early treatment

Correspondence:

Dr D. N. Poller, Department of Pathology, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, UK.

Tel.: +44(0)2392 286458; Fax: +44(0)2392 286493;

E-mail: david.poller@porthosp.nhs.uk

of differentiated tumours necessarily improves overall patient outcome.

Thyroid histopathology

The histological differential diagnosis of hyperplastic but non-neoplastic nodules and follicular adenomas is not always reproducible^{11,12}, likewise for follicular adenoma and carcinoma¹¹⁻¹³ and the follicular variant of papillary carcinoma¹⁴. With this in mind, it is not surprising that different institutions may have vastly different outcomes for the same cytological diagnoses. In other words, an institution is much more likely to have cytological diagnoses of follicular lesions correspond to resected papillary carcinomas, if they happen to be an institution with a bias towards diagnosing follicular variant of papillary carcinoma. As the histological diagnoses upon which cytological-histological correlations are based are not themselves reproducible, making comparisons from the published literature is extremely difficult.

Criteria for adequate FNAC and calculations of sensitivity and specificity

Criteria used to determine adequacy of thyroid FNAC vary^{15,16} and inadequate FNAC results are often treated differently in various published series. In some series patients with cysts are excluded from overall calculations of sensitivity and specificity, in others not. The same applies to patients with incidental carcinomas on histology and patients not undergoing surgery. Consistent study inclusion and exclusion criteria are required for comparison of thyroid histological and FNAC findings. Without this it is impossible to easily compare the results of thyroid FNAC between different institutions.

Onsite adequacy assessment and interpretation

While some centres perform onsite assessment of specimen adequacy at the time of aspiration¹⁷⁻²¹ this practice is not universal. The advantage is that immediate re-aspiration can be performed if required, either because insufficient material is present for cytological interpretation or because more material is needed for ancillary studies such as flow cytometry. Most reports show that onsite adequacy assessment reduces the number of inadequate FNAC¹⁷⁻²⁰ and reduces the clinic re-attendance rates for some patients. As this service can be provided by a

biomedical scientist or cytotechnologist, it does not necessarily require the presence of a cytopathologist in the clinic^{18,19}, saving valuable cytopathologist's time and allowing deployment elsewhere. The few published studies comparing onsite adequacy assessment by cytotechnologists and cytopathologists show broadly similar results. In one study, 93% of FNAC aspirates were judged correctly as adequate by a cytotechnologist as compared with 97% by a cytopathologist.¹⁹ Another study of 323 patients showed lower non-diagnostic rates for palpation guided FNAC, 6.8% inadequate with onsite adequacy assessment and 16.7% without, although there was no significant difference in the inadequacy rate for onsite adequacy assessment with ultrasound (US)-guided FNAC, 4.5% inadequate compared with 7.1% without.¹⁸ The authors also noted that onsite adequacy assessment for US-guided FNAC was useful in reducing the inadequacy rate if the aspirating radiologist was less experienced.¹⁸ Ceresini *et al.*²⁰ also showed a very low FNAC inadequate rate with onsite adequacy assessment by a cytopathologist. By contrast O'Malley *et al.*²¹ were unable to show any benefit from onsite adequacy assessment.

There has also been a recent trend towards increased use of onsite FNAC interpretation, taking the assessment of adequacy one step further. This also allows for immediate reaspiration if required, and, as it cannot be performed by a cytotechnologist, it allows the cytopathologist to review the case notes or discuss the case with the clinician.

The UK National Institute for Clinical Excellence (NICE) in its 2004 publication entitled *Improving Outcomes in Head and Neck Cancers* recommends that '.... there should be an experienced onsite cytologist who can provide FNAC in the clinic to determine the nature of the lump: however this may take some time to achieve and interim arrangements may be necessary....'.²² This guidance advocates onsite thyroid FNAC interpretation although the review panel did not assess other methods of improving thyroid FNAC efficacy²³ such as employing cytotechnologists to provide an onsite adequacy assessment with later rather than in-clinic reporting of thyroid FNAC.^{18,19}

Onsite interpretation is costly and time consuming. One large institution that routinely performs onsite interpretation of thyroid FNAC quotes a technical and professional cost in 2002 of US\$1743 (£884, €1341) and a total institutional cost of \$3096 (£1571, €2383) per single aspirate.²⁴ Another study showed that to improve the adequacy rate from 47% to 67% by

onsite interpretation required an additional 'cost' of 220 minutes of a cytologist's time per additional adequate specimen, and recommended that in clinic adequacy assessment should only be used under special circumstances.¹⁷

The disadvantages of onsite interpretation are that up to 5–10% of diagnoses may eventually be changed and so initial interpretations should not be acted upon unless clinically necessary. The pathologist working in the clinic typically interprets only part of the sampled material, and does not have the benefit of other resources, such as his colleagues and checking by two cytologists²⁵ required for interpretation of difficult cases. Finally, some pathologists may not feel entirely comfortable rendering diagnoses based only on air-dried Diff-Quik™ (Dade Behring SA, B-1070, Brussels, Belgium) stained material. At the time of writing, we do not offer onsite thyroid FNAC assessment in Portsmouth.

Individual institutions should evaluate the use of onsite interpretation and decide, preferably at a multidisciplinary level, whether the value of onsite interpretation justifies the resources required and the expense, and, if so, how the cytopathology staff can be recruited and trained to undertake this work and how cytopathologists will be reimbursed for their time.

Other methods of service improvement e.g. improving the quality of clinical information provided to the cytologist also merit consideration as misleading clinical information is a known pitfall.²⁵ In Portsmouth, we are currently about to trial a detailed thyroid FNAC cytology request form (Figure 1) to see if this improves the quality of the clinical information available to the cytologist.

The use of liquid-based cytology

Many centres now use Thin-Prep™ (Cytoc UK Ltd., Crawley, UK) or other liquid-based cytology (LBC) methods for thyroid FNAC. The published diagnostic results seem comparable to those obtained with conventional FNAC^{26–29} although colloid is not as easy to visualize, and cytological criteria have to be modified as cytological features of LBC preparations are different from conventional smears.^{28,29} LBC allows for easier specimen collection and preparation in general, and reduces the variability of smear quality, artefact, etc., encountered with conventional preparations. A definite learning curve has also been noted, laboratories showing an increase in numbers of indeterminate diagnoses upon first implementing

LBC.³⁰ Whether LBC techniques will become standard for thyroid FNAC remains unclear.

The use of US-guided FNAC

The majority of thyroid FNA are now performed using US guidance. The method has nearly become obligatory at some centres. This allows for better sampling of smaller or multiple nodules compared to freehand FNAC.^{31–33} Certain features are predictive of malignancy e.g. hypoechogenicity, irregular margins, presence of calcifications and absence of a hypoechoic rim³⁴. Its disadvantage is also that it requires an operator experienced in US and an onsite US machine.

Reporting

Thyroid FNAC allows binary triaging for surgery, to enable a decision to operate or not, albeit with some subtleties as some cases may require reaspiration or reassessment after a period of time. The reporting of thyroid FNAC, however, is in many cases not binary. Various diagnostic category systems for reporting FNAC have been reviewed recently by Dr Helen Wang.³⁵ In Portsmouth, we have used our own in-house system (Thy1, Thy2, Thy3, Thy4 and Thy5) since the late 1990s.³⁶ This was because when our thyroid FNAC cytology service was introduced in 1996, we found that surgical and medical colleagues had difficulty understanding some of the complexities of our reporting, which then led to some cases of inappropriate clinical management, e.g. repeat FNAC rather than excision of follicular neoplasms. Other centres within the UK such as Newcastle have also developed their own in-house reporting systems for thyroid FNAC.³⁷ The British Thyroid Association (BTA) and UK Royal College of Physicians (UKRCP) published its thyroid FNAC reporting guidelines in 2002.³⁸ These also use Thy1, Thy2, Thy3, Thy4 and Thy5 terminology although the BTA/UKRCP guidelines differ from our own in-house system.³⁹ Proponents of reporting systems believe that a categorical reporting system makes the cytology diagnoses easier to understand and assists in clinical decision making and audit.³⁵ Detractors argue that the multiplicity of reporting systems seems random and confusing and that simplified reporting systems do not necessarily include all the relevant diagnostic information that is available. Wang, after reviewing all the relevant literature has also recently proposed yet another probability-based reporting system.³⁵

Thyroid FNA Ultrasound and Cytology Assessment Form

Patient Name:..... NHS Number:.....
 Hospital Number:..... Hospital/Clinic:.....
 Date of Birth:..... Aspirator:.....
 Address:..... Signature:.....
 Date:.....

General clinical impression

Clinically suspicious Yes No If Yes give details

Previous thyroid surgery Yes No

If so what type, when, and final diagnosis.....

Thyroid autoantibodies Yes No Not known

Thyroid status Euthyroid Hypothyroid Hyperthyroid Not known

Previous thyroid FNA Yes No Not known

If yes give diagnosis, date and place

Type of nodule	Site	Nature
Solitary <input type="checkbox"/>	Right lobe <input type="checkbox"/>	Solid <input type="checkbox"/>
Dominant nodule in MNG <input type="checkbox"/>	Left lobe <input type="checkbox"/>	Cystic <input type="checkbox"/>
Other nodule in MNG <input type="checkbox"/>	Isthmus <input type="checkbox"/>	Mixed solid and cystic <input type="checkbox"/>

Maximum diameter (mm).....

US features

Microcalcification Yes No Not sure

Irregular calcification Yes No Not sure

Hypoechoogenicity Yes No Not sure

Abnormal vascularity Yes No Not sure

Level of ultrasound suspicion Low High Not sure

Enlarged cervical nodes Yes No

If yes: Right neck level(s)..... Left neck level(s)

FNA technique 23G 25G

Number of passes.....

Figure 1. Redesigned combined ultrasound/cytology specimen request form with tickboxes (also courtesy of Dr E. A. Tilley, Consultant Radiologist).

The simplification of thyroid reporting into five categories, whether numbered or purely descriptive may increase the reproducibility of diagnosis and it seems inherently logical. In thyroid FNAC there are (i) inadequate or non-diagnostic aspirates which require retesting; (ii) obviously benign aspirates, e.g. colloid nodules or aspirates of thyroiditis; (iii) aspirates of processes which cannot be fully classified by FNAC as they require histological assessment for actual classification such as aspirates of follicular patterned lesions other than follicular variant of papillary carcinoma; (iv) aspirates showing some but not all features of malignancy, e.g., cell clusters with enlarged and grooved nuclei without true pseudoinclusions; and (v) obviously malignant aspirates.

The vast array of diagnostic nomenclature currently in use can usually be made to fit into these systems and thus easily explained to clinicians. There is now a need for a more unified approach to the reporting of thyroid FNAC. This would allow for better assessment of how FNAC diagnoses relate to therapy and outcome and for the development of truly evidence-based treatment recommendations.

Value of multidisciplinary team review

The thyroid cytopathologist should work as part of a multidisciplinary site-specific team or work closely with other cytologist team members.²² Regular review and audit of individual cytologists' results and slides should occur at team meetings. This is important because thyroid cytology results are often not binary, to operate or not to operate, and in many cases there is diagnostic uncertainty which can be resolved by case discussion at multidisciplinary team (MDT) meetings. One recent study confirming the importance of MDT review showed intra- and inter-observer disagreement in around 25% of cases.⁴⁰ It is also clear that in a well functioning thyroid MDT differences in MDT final histological diagnosis can and will occur in a significant proportion of cases. One report showed an 18% rate of discordance in the final histological diagnosis between the referral and the final MDT review diagnosis.⁴¹

Putting it all together: 'process re-design'

A study from the USA by Raab *et al.*⁴² recently described reduction of the false-negative rate for thyroid FNAC from 41.8% to 19.1%, their non-diagnostic rate increasing from 5.8% to 19.8%, and an

increase in overall sensitivity from 70.2% to 90.6%. Raab *et al.* used standardized diagnostic terminology, an adequacy scoring system, a non-specific diagnostic category and an immediate interpretation service, with histological assessment as the benchmark. This study showed a reduced rate of diagnostic errors and improved the overall efficacy of the diagnostic process in their clinic setting.

A simplified reporting scheme would, undoubtedly, have to address the assessment of adequacy and an acceptable rate of inadequate diagnoses could then be determined. At the present time there is no accepted definition of what constitutes an inadequate thyroid FNAC, or how cystic thyroid lesions should be classified.

Molecular testing

At the current time molecular testing is of limited use. In the future, if techniques improved, given the positive predictive value of malignant or suspicious FNAC diagnoses and the negative predictive value of benign diagnoses, such cases would likely not require further testing. Sampling issues with inadequate samples would generally render negative molecular testing in such cases unhelpful and, given that molecular abnormalities can be found in benign thyroids (e.g. *ret/ptc* rearrangements in Hashimoto thyroiditis),⁴³ positive testing may also be of limited value with inadequate samples.

Molecular testing could be useful for indeterminate samples, akin to high-risk HPV testing if the method was extremely sensitive and negative testing could exclude papillary or follicular carcinoma. The current best candidates for such testing are the *braf* and *ras* genes which are mutated in a percentage of papillary and follicular carcinomas respectively.⁴⁴ However, the testing for both would not currently capture all cases diagnosed as cancer by histology. DNA microarrays may also have an important role in the future as microarray studies show differential expression of genes in follicular adenomas and follicular carcinomas.⁴⁵ The understanding of the molecular pathways of thyroid cancer biology will need to advance substantially before molecular testing can be used with thyroid FNAC.

Conclusion

This brief review discusses recent developments in thyroid FNAC and offers some suggestions for

improving its overall diagnostic efficacy. While there is already much published literature on thyroid FNAC, the challenge for the future will be to develop easily applicable diagnostic methods for preoperative assessment that are justified in terms of scarce consultant cytological resources and cost/benefit to patients. In an attempt to address many of the issues discussed in this review the United States National Cancer Institute (NCI) is organizing a state of the science conference to be held in Bethesda, Maryland on October 22–23, 2007.⁴⁶ There is also an associated web-based internet discussion forum, which will probably have closed by the time of publication of this article.

For thyroid FNAC the two key areas are (i) whether or not onsite FNAC thyroid assessment is to be provided and if so how, and by whom, and (ii) the use of FNAC diagnostic categories. As much of the claimed added value of onsite thyroid FNAC assessment appears to be related to (i) the increased clinical information provided to the cytologist and (ii) the ready feasibility of re-aspiration if necessary without repeat clinic attendance, both could be achieved using a combination of a more detailed cytology specimen request form in combination with cytotechnology staff to assess specimen adequacy, without necessarily requiring the presence of a consultant cytologist in the clinic. The adoption of a cytology reporting style that incorporates a diagnostic category system without dispensing with a free text report allows for the unambiguous communication of the therapeutic action required. While molecular testing holds much promise, at this moment in time we would not advocate its routine use.

Acknowledgment

The authors are grateful to various colleagues in Portsmouth, and also to Dr Sarah Johnson for constructive comments during the preparation of this article.

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