Contribution of fine needle aspiration cytology to diagnosis and management of thyroid disease

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Abstract
Aims: To determine the role of fine needle aspiration cytology (FNAC) in the diagnosis and management of thyroid disease.

Methods: Clinical histories of 144 patients who had undergone FNAC of the thyroid were analysed. Clinical presentation, non-invasive investigations including hormone assays, ultrasound, and isotope scan procedures were compared with FNAC diagnoses in all cases and with histological diagnosis in the 28 cases (19%) that had undergone surgery. Clinical management was decided upon combining all of the above investigations. The relative contribution of the FNAC was divided into: essential, additional and non-contributory, misleading.

Results: FNAC diagnoses included: 29 (16%) benign colloid goitre, 56 (39%) benign cystic goitre, 24 (17%) thyroiditis, and 22 (15%) neoplasms. Nineteen (13%) of the specimens were unsatisfactory. When compared with clinical diagnoses based on non-invasive diagnostic investigations FNAC represented no improvement on the diagnosis of benign colloid/cystic goitre (55% v 54% respectively). It represented an improvement on the diagnosis of thyroiditis (9% v 17% respectively). FNAC decreased clinically suspicious lesions in which 22 neoplasms were diagnosed from 37% to 15%. Eleven patients with neoplasms underwent surgery and neoplasms were confirmed histologically. Others including lymphoma, metastatic carcinoma, and anaplastic carcinoma were managed conservatively. There were four false negative FNAC diagnoses (3%) in clinically suspicious lesions, found on histology to be benign follicular adenomas.

Conclusions: FNAC had an essential role in the diagnosis and management of 23% of our patients, a confirmatory role in 61% of patients, a non-contributory role in 13% when specimens were inadequate, and was misleading in 3% where results were false negative. The positive identification of thyroiditis and neoplasia stands on its own as a justification for FNAC.

FNAC was first used as a method of diagnosing thyroid disease by Soderstrom and Franzen in the 1950s and 1960s. Since then it has been accepted in many countries. However, apart from at a few centres, FNAC of the thyroid has not been widely used in Britain.

Being a non-endemic area, thyroid disease in Britain is diagnosed mainly with the aid of non-invasive diagnostic procedures and managed conservatively or surgically. The aim of our study was to establish the role of FNAC in the clinical management of thyroid disease. In particular, we were interested in the impact of the introduction of the FNAC on the decreased rate of surgery in clinically suspect thyroid lesions, not only in solitary nodules but also in multinodular and diffuse goitre.

Methods
During the period 1986–1990 (four years) FNAC was performed on 163 patients with thyroid disease. Clinical follow-up was available on 144 of these patients; 19 (11.6%) were lost to follow-up. The female:male ratio of patients in this series was 5:1. The mean age of females was 47.8 years (7–86 years) and males 54.3 (24–74 years).

Methods used in this study included: clinical presentation; non-investigations (thyroid function tests, immunological studies, ultrasound, and isotope scan of the thyroid), FNAC, surgery, and histology.

CLINICAL PRESENTATION
These included symptoms and signs, duration of symptoms, family history of thyroid disease, and history of previous radiotherapy to the neck. Symptoms and signs related to thyroid gland were: solitary nodule, multinodular and diffuse goitre, compression of other structures in the neck, hoarseness, cough, pain, dysphagia, and symptoms related to changed functional state of the thyroid.

NON-INVASIVE INVESTIGATIONS
These included thyroid function tests, immunological studies, ultrasound, and isotope scans of the thyroid. Thyroid function tests were used to determine blood concentrations of thyroid hormones. T4, free T4 and free T3 were measured by radioimmunoassay and TSH was measured by immunoradiometric assay (IRMA). Depending on these results patients were considered euthyroid, hyperthyroid, and hypothyroid.

Immunological studies included serum assays of thyroid antibodies. Antibodies were measured by radioimmunoassay and antithyroglobulin (tg) and antimicrosomal (tm) antibodies were
measured using a particle-agglutination method; titres of $>1/80$ for $\text{tg}$ and $>1/1600$ for $\text{tn}$ were regarded as significant.

**Ultrasound examination** was performed with an Accuson 128 machine with a high frequency linear array transducer (7-5 MHz) to obtain high resolution images. The echo texture and the echo pattern of thyroid lesions were observed. Based on echo texture, thyroid lesions were classified as cystic, solid, or mixed. Special attention was given to the pattern of degeneration in the mixed nodules. Radioisotopic evaluation of the thyroid gland was always done with radioactive iodine $^{113}$-$^{123}$

Twenty megabecquerels ($20 \text{ Mbq} = 541 \text{ Ci}$) was given by mouth to the patients. Four hours later images of the neck were acquired using an Anger gamma camera/computer system in order to calculate uptake values and to study thyroid morphology. The normal range for the 4 hour thyroid uptake was from 10% to 25%. Values below and above these limits were consistent with, respectively, hypo- and hyperthyroidism. The study of thyroid morphology enabled the identification of areas with either focal decrease ("cold nodules") or focal increase ("hot nodules") in the $^{113}$ uptake. Lesions considered as **clinically suspicious** were those fulfilling one or more of these criteria: single nodule or an altered nodule in a multinodular goitre, present for a relatively short time (months rather than years), solid and single on ultrasound, "cold" on isotope scan, euthyroid, and antibody negative.

**FNAC of Thyroid gland**

This was performed in each patient either by the clinician or, in the majority of cases, by the cytopathologist using a standard technique. After a brief explanation of the procedure and a request not to swallow or speak during the procedure, the patient was put in a supine position with the neck extended. No local anaesthetic was used. The fine needle aspiration cytology was performed using a 23-gauge needle attached to a 20 ml disposable syringe and Cameco syringe holder. An average of one attempt per nodule or lobe was performed usually resulting in four direct smears which were subsequently stained with routine cytological stains (air dried smears, May-Grunwald Giemsa stain).

Cytological smears were interpreted as benign colloid goitre, benign cystic goitre, thyroiditis (subacute and chronic), neoplasms, and unsatisfactory. Neoplasms included follicular neoplasms (combined benign and malignant), papillary carcinoma, medullary carcinoma, metastatic carcinoma, and lymphoma. Specimens with a high admixture of blood and no thyroid epithelium were considered unsatisfactory for reporting. Interpretation of results as "suspicious" was avoided in this study. Surgery was performed in 28 out of 144 patients (19.5%). Histological categories included: 12 benign goitre, one thyroiditis and 15 neoplasms including follicular adenoma, papillary carcinoma, medullary carcinoma, and metastatic carcinoma.

**Clinical management**

Clinical management was decided upon combining clinical diagnosis, results of non-invasive procedures, FNAC, and in some cases histological diagnosis. Since our starting point in the study was the patients who had undergone the FNAC of the thyroid, we were particularly interested in the contribution the FNAC diagnosis had to the ultimate clinical management. This contribution was arbitrarily divided into: essential, additional, and non-contributory/ misleading with percentage figures for each category.

Patients who have not undergone surgery were managed conservatively with a 6-12 monthly clinical review and possibly ultrasound examination. T4 suppression was not used. Patients were advised to return if there was an alteration in the size of the lesion.

Statistical analysis of accuracy, sensitivity, specificity, positive, and negative predictive values of the FNAC have been calculated only for those patients who had histological confirmation.

**Results**

The major presenting symptom in all of the 144 patients who have subsequently undergone FNAC was goitre or multiple nodules (table 1). Of these, 112 (78%) had a solitary nodule, 24 (17%) a multinodular goitre, and eight (6%) a diffuse goitre (table 1). Other signs and symptoms at clinical presentation were less frequent: pain in 11 (8%), dysphagia in six (4%), hoarseness in five (3%), inspiratory stridor in four (3%), cough in two (1%), and palpable lymph nodes in four (3%). Patients gave a history of goitre or nodule being present for one year (42%), less than three months (39%), and between three months and one year (19%).

Family history of thyroid disease was positive in nine patients (6%) and five (3%) had a history of previous radiotherapy to the neck.

**Thyroid function tests**

These were performed in 124 patients (86%). These have shown 88% to be euthyroid, 9% hyperthyroid, and 3% hypothyroid (table 2). Hyperthyroidism occurred in three patients with a solitary nodule, two patients with diffuse goitre, five patients with thyroiditis, and one patient clinically suspected of malignancy.

<table>
<thead>
<tr>
<th>Table 1 Thyroid signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of patients</strong></td>
</tr>
<tr>
<td><strong>Goitre</strong></td>
</tr>
<tr>
<td>Solitary nodule</td>
</tr>
<tr>
<td>Multinodular</td>
</tr>
<tr>
<td>Diffuse</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Dysphagia</td>
</tr>
<tr>
<td>Hoarseness</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Inspiratory stridor</td>
</tr>
<tr>
<td>Resulting from increased hormonal concentrations</td>
</tr>
<tr>
<td>Resulting from decreased hormonal levels concentrations</td>
</tr>
</tbody>
</table>
Hypothyroidism occurred in one patient with solitary nodule, two patients with thyroiditis, and one patient with clinically suspect malignancy.

**IMMUNOLOGICAL TESTS**

They were evaluated in 65 patients (45%). Antibody assays were positive in 36% of cases. Of these, two were solitary nodules, four goitres, 11 thyroiditis, and seven suspected of malignancy. Tests were negative in 63% of cases, including 18 solitary nodules, 10 goitres, two thyroiditis, and 11 suspected malignancies.

**ULTRASOUND**

Ultrasound examination was performed in 76 patients (53%). It showed a cystic echo texture in 19 cases (25%), a solid echo texture in 26 cases (34%), and a mixed echo texture in 31 cases (41%). Five of the 19 cystic lesions, 13 of the 26 solid lesions, and nine of the 31 mixed lesions were thought clinically to be suspicious of malignancy.

**ISOTOPE SCAN**

An isotope scan was performed in 51 patients (35%). Scan result was normal in 16% cases, showed an increased uptake in 12%, and a decreased uptake in 72% patients. A "hot" nodule was present only in benign lesions; 14 of the 37 "cold" nodules were clinically suspicious of malignancy, and the remaining 23 were clinically benign lesions (five thyroiditis, 10 goitre, and eight solitary nodules).

**REFERRAL FOR FNAC**

This was based on clinical presentation and/or results of non-invasive diagnostic procedures.

FNAC diagnoses included: benign colloid goitre in 29 (16%), benign cystic goitre in 56 (38%), thyroiditis in 24 (17%), and neoplasms in 22 (15%) patients (table 3). Nineteen (13%) specimens were considered unsatisfactory for cytological interpretation. FNAC diagnosis of thyroiditis included 23 Hashimoto's and one subacute thyroiditis. Neoplasms included follicular neoplasm (eight), papillary carcinoma (four), metastatic carcinoma (four), anaplastic carcinoma (three), medullary carcinoma (two), and non-Hodgkin's lymphoma (one). When compared with clinical diagnosis, FNAC confirmed original clinical diagnosis (supported by non-invasive diagnostic procedures) in 57 out of 78 patients considered to have colloid goitre and/or benign cystic goitre, 11 out of 13 patients considered to have thyroiditis, and 20 patients out of 53 with clinically suspected neoplasia (table 3). Total agreement with the clinical diagnosis was achieved in 88 out of 125 patients (70%) excluding those with unsatisfactory FNAC specimens. FNAC differed from the initial clinical diagnosis in 37 patients (38%). These included: eight patients with colloid goitre, originally clinically suspected to be neoplasia, 14 patients with benign cystic goitre either originally diagnosed as thyroiditis (one patient), or suspected neoplasia (13 patients). Thirteen patients with an FNAC diagnosis of thyroiditis were either originally...
Table 4 Patients with FNAC/clinical diagnosis who underwent surgery

<table>
<thead>
<tr>
<th>FNAC/clinical diagnosis</th>
<th>Surgery not performed</th>
<th>Surgery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAC* Benign goitre (colloid/cyst)</td>
<td>81</td>
<td>12*</td>
<td>93 (65%)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>24</td>
<td>1</td>
<td>25 (17%)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>11</td>
<td>11</td>
<td>22 (15%)</td>
</tr>
<tr>
<td>Suspected malignancy†</td>
<td>0</td>
<td>4</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>110 (80%)</td>
<td>28 (19%)</td>
<td>144</td>
</tr>
</tbody>
</table>

*Clinical diagnosis: suspected malignancy/FNAC benign.
†Clinical diagnosis: suspected malignancy/FNAC unsatisfactory.

Table 5 Comparison of the histological results with FNAC/clinical diagnosis based on non-invasive diagnostic procedures

<table>
<thead>
<tr>
<th>FNAC/clinical diagnosis</th>
<th>Histological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign goitre</td>
</tr>
<tr>
<td>Benign goitre*</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>0</td>
</tr>
<tr>
<td>Suspected malignancy†</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (43%)</td>
</tr>
</tbody>
</table>

*Clinically suspicious/FNAC benign.
†Clinically suspicious/FNAC unsatisfactory.

diagnosed as a solitary nodule (five patients) or suspected neoplasm (eight patients). Two patients with an FNAC diagnosis of neoplasm had an original diagnosis of solitary nodule. FNAC was considered unsatisfactory for diagnosis in 19 patients (13%), four of whom were clinically suspected of having neoplasm. These were later biopsied.

HISTOLOGICAL DIAGNOSIS

Histological diagnosis was available in the 28 (19%) of patients who underwent surgery (Table 4). The indications for surgery were certain neoplasms and lesions which were clinically suspicious of malignancy after combined assessment of diagnostic tests. These included: 12 patients with FNAC diagnosis of benign goitre, one thyroiditis, 11 neoplasms, and four with an unsatisfactory FNAC result. The 12 cytologically benign lesions which were biopsied were all solitary, solid nodules. The remaining nine of the 21 clinically suspicious and cytologically benign lesions are being managed conservatively.

Since the aim of our study was to establish the role of FNAC in the diagnostic process of thyroid disease, we were particularly interested in the comparison of the histological results with FNAC/clinical diagnosis based on the non-invasive diagnostic investigations (Table 5). Eleven FNAC diagnoses of neoplasms were confirmed histologically. Four out of 12 FNAC benign lesions which were biopsied were found to be follicular adenomas. Four patients with clinically suspicious and unsatisfactory FNAC results proved to be benign. One case of thyroiditis was confirmed histologically. Statistical analysis of FNAC diagnosis of thyroid lesions is shown in Table 6. When correlated with histological diagnosis available in 28 cases, FNAC showed accuracy of 83%, sensitivity of 73%, and specificity of 100%.

Discussion

The diagnostic role of the FNAC over and above the non-invasive diagnostic procedures in benign, clinically suspicious, and malignant lesions of the thyroid can be classified into: essential, additional, and non-contributory/misleading depending on the impact that FNAC had on the clinical management.

BENIGN DISEASE

In the large series of 6300 thyroid aspirates from the Mayo Clinic, benign disease represented 65% of the total findings. This included both thyroiditis and benign colloid/cystic goitre. Similarly, in the series of Schenck, negative findings represented 81.5% of the 1000 thyroid aspirates. However, in these studies there is no reference to the relative contribution of the benign FNAC diagnosis to the ultimate management. In our series the FNAC, when compared with the initial clinical diagnosis based on non-invasive investigations, represented no improvement on the original diagnosis of benign colloid/cystic goitre (55% vs 54% respectively) and can be considered as additional to the diagnosis. On the other hand it represented an improvement on the diagnosis of thyroiditis (9% vs 17%) and can be considered as essential in those cases. This is similar to the experience of others who found that up to 63% of thyroiditis had no clinical diagnostic features.

CLINICALLY SUSPECT LESIONS

Solitary nodules which are occasionally clinically suspect and cannot be clarified by means of non-invasive investigations, can be diagnosed by FNAC. In our series FNAC meant a decrease of clinically suspect lesions from 37% to 15.4% and can therefore be considered as essential in those cases. In the experience of other authors approximately 3–11% of thyroid aspirates are cytologically suspicious. This group includes diagnoses “consistent with follicular neoplasm”, “consistent with Hurthle cell neoplasm” and “suggestive of papillary carcinoma". Suspicious FNAC results require

Table 6 Statistical analysis of FNAC diagnosis of thyroid lesions

| Statistical analysis of FNAC diagnosis | Total No cases | Accuracy | Sensitivity | Specificity | PPV | NPV | FN
<table>
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<tbody>
<tr>
<td>FNAC/histological diagnosis</td>
<td></td>
<td>tp + fn</td>
<td>tp + m + fn</td>
<td>tp + fn</td>
<td>tp + m + fn</td>
<td>tp + fn</td>
<td>tp + fn</td>
</tr>
<tr>
<td>Positive</td>
<td>144/24*</td>
<td>83-3%</td>
<td>73-3%</td>
<td>100%</td>
<td>100%</td>
<td>69-2%</td>
<td>26-6%</td>
</tr>
<tr>
<td>False p</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>True n</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>False n</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Four patients who have undergone surgery but with a FNAC diagnosis of unsatisfactory are excluded.
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histological confirmation. In the Mayo Clinic series, 27% of the cytologically suspicious lesions proved to be malignant.2

NEOPLASMS
Out of 53 clinically suspicious cases in our series FNAC led to diagnosis of tumour in 20. Two further neoplasms were diagnosed in clinically unsuspected cases of solitary nodules. However, neoplasm was not diagnosed in four cases of follicular adenoma which were cytologically benign but clinically suspicious.

The false negative rate of thyroid FNAC ranges between 2% to 33%.41 False positive results are rare, one of 221 cases in the Mayo Clinic series.28

In summary, we have proved FNAC to have an essential role in the diagnosis and management of 23% of our patients, a confirmatory role in 61% of patients, a non-contributory role in 13% when specimens were inadequate and a misleading role in 3% where the results were false negative. The positive identification of thyroiditides and neoplasms stands on its own as a justification for FNAC.

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31 Suen KC. How does one separate cellular follicular lesions of the thyroid by fine-needle aspiration biopsy? Diagn Cytopathol 1988;78:81-82.
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