

The Accuracy of Fine Needle Aspiration at Identifying Thyroid Malignancy in Tayside

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ABSTRACT

Introduction

Thyroid lumps are common with up to 8% of the adult population having a palpable lump and up to 70% having an incidental nodule found on ultrasound. Although most thyroid nodules are benign, a significant number are malignant and therefore need to be investigated thoroughly using fine needle aspiration (FNA) +/- ultrasound.

Methods

This study aims to compare FNA results to histological findings after excision to ascertain the accuracy of FNA diagnosis in NHS Tayside. Included in the study were all patients who had undergone surgery to remove their thyroid nodule in Tayside between 2003 and 2011 after being investigated using FNA (n=273).

Results

119 patients had benign results on FNA with 16 of these found to be malignant on histology after excision. This gives a false negative rate of 13%. 14 patients had malignant results on FNA with all of these found to be malignant on histology after excision, giving a false positive rate of 0%. All other FNA results were either non-diagnostic or borderline. The sensitivity and specificity of FNA was therefore found to be 100% and 30% respectively.

Conclusion

In Tayside, FNA is accurate at predicting malignancy but has a high false negative rate when predicting benign nodules.

Background

Thyroid lumps are common with as much as 8% of the adult population having a palpable lump¹ and up to 70% having an incidental nodule found on ultrasound.² In Tayside, all thyroid nodules requiring secondary care are referred to Ninewells Hospital, Dundee and may be seen by an Endocrinologist, General Surgeon or Otolaryngologist (ENT).

Most thyroid nodules are benign with Deandrea et al³ reporting 33% malignancy for a solitary nodule and 22% for a dominant nodule in a multinodular goitre. Therefore, urgent referral is not required unless there are worrying features present. Worrying features as indicated by the British Thyroid Association⁴ include:

- Family history of thyroid cancer
- History of previous irradiation or exposure to high environmental radiation
- Child with a thyroid nodule
- Unexplained hoarseness or stridor associated with goitre
- Painless thyroid mass enlarging rapidly over a few weeks
- Palpable cervical lymphadenopathy
- Insidious or persistent pain lasting for several weeks.

Patients with none of these red flag symptoms should be seen in a specialist thyroid clinic within 4 weeks of referral for assessment, patients with these symptoms should be seen within 2 weeks and patients complaining of stridor should be seen urgently on the same day.³

Assessment of a Thyroid Lump

Assessment of a thyroid lump begins with a detailed history and clinical examination which should include the thyroid, surrounding lymph nodes in the neck and a systemic examination.¹ Patients should have their Thyroid Function Tests (TFTs) checked;^{3,4} Thyroid Stimulating Hormone (TSH), Thyroxine (T4) and Triiodothyronine (T3). These can be assessed in General Practice. If the results show hyperthyroidism, the patient should be referred to Endocrinology for assessment. All patients with thyroid lumps are then assessed using Ultrasound +/- Fine Needle Aspiration (FNA) to assess the risk of malignancy and determine whether or not surgery is appropriate.^{1,3,5-7}

Fine Needle Aspiration [FNA]

FNA may be carried out by a surgeon, cytopathologist, endocrinologist, radiologist or an oncologist provided they have adequate training and experience and have continued to practice their skills.^{3,8-10} FNA is performed using a 25 gauge needle which is passed into the nodule under aseptic conditions. The needle is then rotated and fluid aspirated if present. The sample can then be sent to pathology for assessment using either a liquid medium or smeared on glass slides.¹¹ The results are

reported using the following diagnostic categories as stated in the British Thyroid Association's Guideline on the Management of Thyroid Cancer:

- **Thy1 – Non Diagnostic**
Non-diagnostic (inadequate or where technical artefact precludes interpretation; adequate smears usually contain six or more groups of over 10 thyroid follicular cells, but the balance between cellularity and colloid is more important).
- **Thy2 – Non Neoplastic**
Non-neoplastic (with the descriptive report documenting the features consistent with a colloid nodule or thyroiditis). Cysts may be classified as Thy2 if benign epithelial cells are present.
- **Thy3 – Follicular lesion; suspected follicular neoplasm; worrying features (indeterminate)**
 - (i) Follicular lesion/suspected follicular neoplasm. While some of these will be tumours, many will be shown to be hyperplastic nodules on surgical excision. The descriptive text will indicate the level of suspicion of neoplasia.
 - (ii) There may be a very small number of other cases where the cytological findings warrant inclusion in this category rather than Thy2 or Thy4 (eg worrying features but cells too scanty to qualify for Thy4, repeat FNAC advised). The text of the report should indicate the worrying findings
- **Thy4 – Suspicious of Malignancy**
Suspicious of malignancy (suspicious, but not diagnostic, of papillary, medullary or anaplastic carcinoma, or lymphoma).
- **Thy5 – Diagnostic of Malignancy**
Diagnostic of malignancy (unequivocal features of papillary, medullary or anaplastic carcinoma, lymphoma or metastatic tumour).

In Tayside, thyroid lumps are investigated and managed using the Nodular Thyroid Disease with normal TSH protocol. This protocol is outlined in Figure 1.

Aims of Research

This project compared individual thyroid FNA sub-categories (Thy 1, Thy 2 etc) outcome to histological findings post surgery to ascertain accuracy of FNA diagnosis in NHS Tayside. Results will then be compared with that reported in the literature.

Methods

Approval for this project was granted by the NHS Tayside Caldicott guardian and Data Protection. On submission of the Caldicott Guardian Approval the Pathology department at our institute provided a list of patients who had definitive histology

on thyroid specimens sent between 2003 and 2011. This list contained the name of the patient, CHI number, date of surgery and histology outcome. All identifiable data was kept password protected throughout the project. Due to the nature of thyroid surgery, some patients had more than one surgical procedure and hence there were multiple entries in the database for those patients. For the purposes of this study only the first surgical procedure resulting in definitive histological diagnosis was included for each patient. The information was then used to construct a large database of thyroid pathology in NHS Tayside using the following headings:

- Name of patient
- CHI number
- Date of Birth
- Ultrasound performed (yes/no)
- Size of single nodule (cm)
- Multinodular goitre present (yes/no)
- Size of dominant nodule in multinodular goitre (cm)
- Ultrasound guided fine needle aspiration (yes/no)
- Result of first FNA
- Result of repeat FNA
- Indication for surgery
- Date of operation
- Operation performed
- Surgeon
- Side of Operation
- Histological result
- Excision (Complete/Incomplete)

In addition to the information provided by pathology, information required to complete the database was identified using the local Electronic Patient Record (EPR) system by entering the patient's CHI number and looking for the corresponding date of surgery on pathology reports, FNA reports and radiology reports. Once the database was complete the information was used to complete a study on FNA results and thyroid malignancy rates in NHS Tayside. Included in this study were all patients who had thyroid surgery for diagnostic reasons or as a consequence of clinical requirement, for example acute airway compromise from a large goitre. From the completed database the preoperative FNA results were identified and compared to definitive histological diagnosis post surgery. Second FNA results where applicable were also analysed.

Results

There were 598 patient entries on the database provided by the Tayside Pathology department. After applying the process described in the method section 325 patients were identified. No patients were excluded.

273 of the 325 patients had FNA performed at least once. Table 1 is a summary of the cytology result of the first FNA performed with percentages calculated (Table 1).

Table 1. Cytology result of first FNA performed with percentages calculated.

Cytology result	Thy1	Thy2	Thy3	Thy4	Thy5	Total
Number of patients	69	119	71	7	7	273
Percentage of Patients (%)	25%	44%	26%	2.5%	2.5%	100%

Of this group of patients that had first FNA cytology results of Thy 1, 2 or 3, 36% (n=93) went on to have a further FNA. Table 2 summarises the cytology results for this group.

Table 2. Number of patients who underwent a repeat FNA and corresponding cytology result with percentages calculated.

Original FNA result (n=patient number)	Number of patients undergoing a second FNA	Percentage repeated (%)	Percentage (%) of patients with repeat FNA category of:				
			Thy1	Thy2	Thy3	Thy4	Thy5
Thy1 (n=69)	41	59%	49%	22%	24%	5%	0%
Thy2 (n=119)	37	31%	11%	65%	19%	5%	0%
Thy3 (n=71)	15	21%	13%	7%	73%	7%	0%

Of the 325 patients included in the study, 90 were diagnosed with a thyroid malignancy. Of these 90 patients, 58 were female and 32 were male. Therefore, the male: female ratio of patients diagnosed with a thyroid malignancy in Tayside is 1: 2. The age range of patients diagnosed with malignancy was 17-91 and the average age 56. The number of patients diagnosed with each sub-type of thyroid malignancy was also extracted from the database and percentages calculated (Table 3).

Table 3. Percentage of patients diagnosed with each thyroid malignancy sub-type.

Type of Thyroid Malignancy	Number of Patients	Percentage (%)
Anaplastic Carcinoma	7	8%
Follicular Carcinoma	12	13%
Hurthle Cell Carcinoma	4	4.5%
Lymphoma	8	9%
Medullary Carcinoma	4	4.5%
Papillary Carcinoma	50	56%
Poorly/undifferentiated Carcinoma	2	2%
Metastatic	3	3

Table 4 correlates the first FNA result with definitive histology post surgery with percentages displayed in the last column. The cytology result and corresponding histology result were used to calculate the following statistical values.

Of patients with an original FNA result of Thy2 the number of false negatives was 16 giving a false negative rate of 13% and a negative predictive value of 86%. Of patients with a FNA result of Thy4/5 the number of false positives was 0 giving a positive predictive value of 100%. Specificity of FNA was calculated as 100% and sensitivity as 30% using the first FNA result.

There were 25 patients with the original FNA outcome of Thy3 and definitive histology of thyroid malignancy. In 14 of these patients the cytopathology report states that the nodule is “probably benign” and in a further 10 that “further investigation is recommended.” Table 5 demonstrates the cytopathologist’s impression of the FNA sample.

Table 4. Cytology result of first FNA and corresponding histology result after excision.

Original FNA result	Number of patients	Number malignant	% malignant
No FNA	52	14	27%
Thy1	69	21	30.4%
Thy2	119	16	13.4%
Th3	71	25	35.2%
Thy4	7	7	100%
Thy5	7	7	100%

Table 5. Cytopathologist’s impression (as stated in Pathology report) of FNA Thy3 samples that were histologically found to be malignant (n=25).

Cytopathologist’s Impression	Number of Patients	Percentage (%)
Probably Benign	14	56%
Further investigation recommended	10	40%
Unstated	1	4%

Discussion

There were 325 patients included in this study all of whom presented to either Endocrinology or ENT with a thyroid lump that resulted in surgical excision. 273 of these patients were investigated using FNA +/- ultrasound scan - the gold standard for investigating thyroid nodules. 52 patients were not investigated using FNA before theatre due to a variety of reasons including worrying features on presentation such as stridor, metastases suggestive of a primary thyroid malignancy or indeed patient choice. That 14 of 52 (27%) of these patients had malignancy on histology is concerning but for complete data on the indication for surgery in these patients, the patient notes would have to be retrieved which is outside the scope of this study.

Comparison of the FNA result with the histology result after excision showed 30% of Thy1 results, 13% of Thy2 results, 35% of Thy3 results and 100% of Thy4 and Thy5 results were malignant on histology. These results are interesting as current literature suggests that 9-12% of Thy1 nodules are malignant^{7,12,13}, in comparison to our study which found 30% of Thy1 results in Tayside to be malignant. This is significantly higher than current literature and may warrant further investigation.

13% of Thy2 results were proven to be malignant lesions on histology which shows there were a number of false negative FNA results. The false negative rate was found to be 13.4% (16 false negatives out of 119 samples), with a negative predictive value of 86%. Literature on this subject varies, with the false negative rate ranging from 4% to 21%.^{2,7,13,14} Ultrasound guided FNA has become common clinical practice in the 10-year period that this study has examined and it is therefore pertinent to assess whether or not this has caused a reduction in the number of false negatives. Thus, further studies examining the issues raised is advisable. The false negatives reported above cannot be commented on fully as these incorporate results from before and after the implementation of ultrasound guided FNA.

The study also shows that 35% of Thy3 nodules were malignant on histology which is in keeping with current literature.^{7,15} Interestingly, of the 25 patients who had a FNA of Thy3 and were subsequently diagnosed with malignancy, 14 were stated as being “probably benign” in the cytopathologist’s report.

100% of Thy4 and Thy5 results were malignant on histology showing there were no false positive FNA results and therefore a positive predictive value of 100%. Literature suggests false positive rates of 0-28%.^{7,14,16} The sensitivity of FNA in Tayside was shown to be 30% and the specificity was 100%. Literature suggests figures of 79-100% sensitivity^{1,16-18} and 67-98.5% specificity¹⁶⁻¹⁸ for FNA.

Therefore, Tayside has a low sensitivity compared to other centres which may need to be looked at in future studies. In total 28% of all thyroid nodules removed were malignant. This is in keeping with current literature which suggests 33%.³ The most common sub-type of thyroid malignancy in Tayside is papillary carcinoma which accounted for 56% of all thyroid malignancies in this study. Other sub-types were much less common; 13% follicular, 9% lymphoma, 8% anaplastic, 4.5% Hurthle cell, 4.5% Medullary, 3% metastatic and 2% were undifferentiated.

The results also show that the non-diagnostic (Thy1) FNA rate in Tayside to be 25%. Current literature varies on this statistic with Yeung et al¹ stating a non-diagnostic rate of 12% and Sellami et al¹⁶ stating 29-51% non-diagnostic samples between two different operators. Finally, this study showed that in Tayside females are twice as likely to develop a thyroid malignancy than males, with a male to female ratio of 1:2. This supports current consensus that females are more likely to get the malignancy than males.¹⁴ The age range of patients in Tayside diagnosed with malignancy was found to be 17-91 with an average age of 56.

Conclusion

In Tayside, FNA is accurate at predicting malignancy in Thy4 and Thy5 sub-categories as all patients in these categories went on to be histologically diagnosed with a thyroid malignancy. The rate of malignancy in the Thy3 sub-category is in keeping with current literature however the rate of malignancy in the Thy2 sub-category is high with a false negative rate of 13%. The rate of non-diagnostic (Thy1) samples in Tayside is also high (25%) which needs to be investigated further. Future studies are required to investigate whether or not Tayside's protocol of assessing thyroid nodules (Fig 1) is accurate enough at predicting which patients are at risk of thyroid malignancy. In order to comment on this, a study will need to be undertaken to look at FNA accuracy before and after ultrasound guidance was introduced as this will give a better picture of current accuracy.

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