

The final outcome of indeterminate cytology of thyroid nodules in a District General Hospital

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SUMMARY: The final outcome of indeterminate cytology of thyroid nodules in a District General Hospital.

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Background. Diagnostic thyroid lobectomy is performed to resolve the dilemma of indeterminate (Thy3) cytology of thyroid nodules. But on final histology most nodules are benign thereby subjecting this group of patients to surgery with its associated risks.

Aim. To determine the proportion of cancers in patients with indeterminate thyroid nodules.

Patients and methods. This is a retrospective observational study of 621 patients who underwent fine needle aspiration cytology (FNAC) of their thyroid nodules over a 60 month period in a district general hospital. Patient demographics, cytology and final histology results were extracted from the hospital database.

Results. On final analysis, 48 patients had an indeterminate cytology (7.7%) and 12 patients had cancer in this group (25%) following diagnostic lobectomy.

Conclusion. Till an alternative robust technology becomes widely available we need to continue to perform diagnostic lobectomy in patients with indeterminate cytology in view of the high incidence of thyroid cancer in this group of patients.

KEY WORDS: Thyroid nodule - Cytology - Indeterminate - Diagnostic lobectomy - Cancer.

Introduction

The American Thyroid Association (ATA) defines a thyroid nodule as a “discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma” (1).

The incidence of thyroid nodules in the United States is approximately 0.1% per year, translating to a lifetime risk of 10% of developing a thyroid nodule. However, the prevalence of thyroid nodules also depends on the mode of detection-by palpation it ranges from 4% to 7%, whereas with high resolution ultrasonography it ranges from 20% to 76% in the adult population (2). The frequency of thyroid nodules increases with age and low iodine intake and in iodine-sufficient parts of the world, palpable thyroid nodules have a prevalence of approximately 1% in men and 5% in women (3). Thyroid nodules can cause thyroid hormone dysfunction or com-

pressive symptoms. But most significantly it's important to exclude malignancy. Depending on the risk factors, about 5-10% of these nodules would have cancer (4). The aged standardised rate of thyroid cancer in 2005 in the UK for males and females in the age group 30-49 was 12.7 per million and 42.3 per million respectively (5). Clinical assessment of thyroid nodules should proceed along the usual lines but should also focus on compressive symptoms, features of thyrotoxicosis and the risk factors for cancer. The clinical risk factors for malignancy are past or family history of thyroid cancer in one or more first degree relatives, exposure to ionizing or external beam radiation in childhood, multiple endocrine neoplasia (MEN), familial medullary thyroid cancer (FMTC) and 18-Fludeoxyglucose (FDG) avidity on Positron Emission Tomography (PET) scanning (1). A finding of rapid growth, hoarse voice, and nodule more than 4 cm in size and, cervical lymphadenopathy should raise suspicion of cancer.

In all patients with thyroid nodules the serum Thyroid Stimulating Hormone (TSH) should be checked. Serum TSH has proven to be an independent risk factor for predicting malignancy in a thyroid nodule. In a study involving 1500 patients with thyroid nodules, the prevalence of malignancy was 2.8 % with a serum TSH

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of <0.4 mU/L and increases to 29% with TSH concentrations >5.5 mU/L (6).

If the TSH is low then the patient needs to have a thyroid uptake scan to look for a toxic nodule. Several publications have recommended that if it's a hot nodule there is no need for FNAC since it's always benign (1). This view has recently been challenged by a study from South Korea. In a retrospective study of 107 patients with increased uptake on thyroid scintigraphy, there were 7 cancers (6.5%) on final histology (7).

Ultrasound is useful to determine if the nodule is solid or cystic, solitary or dominant nodule in a multinodular goitre, size and lymph node status. Ultrasonographic findings of taller than wide on transverse view, infiltrative margins, increased vascularity, hypoechogenicity, irregular outline and microcalcification make a nodule suspect but none of these features are pathognomonic either alone or in combination to confirm a nodule is malignant. Papillary and follicular thyroid cancers have different features on ultrasound scan (8). The predictive value of these characteristics varies widely and hence one should not rely on thyroid ultrasound to diagnose cancer or to select patients for surgery. However, ultrasound findings can be used to select nodules for FNAC.

Fine needle aspiration cytology

FNAC is currently the gold standard diagnostic test for the initial evaluation of a thyroid nodule (along with a serum TSH level) and is a Grade 'A' recommendation by the American Thyroid Association (1). There is variation in the recommendations of the ten international clinical guideline groups on indications of fine needle aspiration of thyroid nodules. For example, the American and British Thyroid Associations (ATA and BTA respectively) recommend fine needle aspiration cytology (FNAC) of nodules without suspicion of more than 0.5mm, the American Association of Clinical Endocrinologists and the European Society of Medical Oncology recommend FNAC of nodules more than 1 cm and the German Association of Endocrine Surgeons and Northern Cancer Network advocate fine needle aspiration in all nodules (9).

Several studies have found FNAC to be a safe, accurate, rapid, cost-effective, and minimally invasive diagnostic tool and complications are extremely rare and could include persistent pain, haematoma, infection, and recurrent laryngeal nerve palsy (10). FNAC is performed using a 23 to 27 gauge (commonly 25 gauge) needles with or without local anaesthesia. Ultrasound-guided FNAC has been found to be superior to clinically-guided FNAC with inadequate sample rates of 14-21% versus 32-50%, respectively, thereby reducing inadequate sampling and need for repeat biopsy (10).

The Bethesda criteria for reporting thyroid cytology were developed by a committee at the National Cancer Institute meeting in 2007. The main aims were to introduce a uniform reporting system to facilitate more reliable interpretation of thyroid cytology and improved communication between members of the multi-disciplinary team involved in the care of patients with thyroid nodules. There are 6 diagnostic categories and each of them is risk stratified for malignancy along with specific recommendations for patient management (11).

In one of the largest series to evaluate the Bethesda criteria-Theoharis et al, there were 3207 FNACs from 2468 patients. Of these 378 (15%) underwent surgery. The positive predictive values for 'suspicious for follicular neoplasm', suspicious, and malignant cytological diagnosis were 34%, 87%, and 100%, respectively. The false-positive rate was 2.2% and the specificity for diagnosing malignancy was 93% (12).

The system in use in the UK is the Royal College of Pathologists' "Thy 1-Thy 5" categories 2007 terminology, first produced in 2002 (13). The principles of categorisation are similar to that in the Bethesda Criteria.

Thy 1: An aspirate is considered adequate if there are at least 6 follicular cell groups with about 10-15 cells in each group. If this criterion is not met or there is no favourable ratio between colloid and cells, it is designated as a non-diagnostic cytology (13).

Thy 2: If the samples fulfil the definition of adequacy i.e. at least six follicular cell groups, each containing 10-15 cells derived from at least two aspirates of a nodule, then it's categorised as Thy 2. Normal thyroid tissue, thyroiditis, hyperplastic nodules and colloid nodules are included in this non-neoplastic category. There should be a descriptive report of the exact pathology. Two non-neoplastic FNAC three to six months apart are sufficient to exclude neoplasia and in the absence of high risk features no further aspiration is needed in this category (13).

Thy 3: This category includes follicular adenomas, follicular carcinomas, Hurthle cell adenoma and carcinoma and, papillary thyroid carcinoma without characteristic nuclear features of cancer. These lesions cannot be reliably distinguished on cytology alone and are classified as Thy3f ('f' for 'follicular'). In the category Thy 3a there is atypia along with a non-diagnostic slide and included in this category are mixed micro- and macrofollicular pattern (approximately equal proportions of each), where a definite distinction between a follicular neoplasm and hyperplastic nodule is difficult. In a solitary nodule with Thy 3 cytology, the risk of malignancy is about 20 % (14, 15, 16). The risk is higher when there are additional risk factors such as large tumours (>4 cm), family history of thyroid cancer and exposure to ionizing radiation in childhood (17, 18). Currently, the only way to resolve the issue of Thy 3 cytology is a diagnostic lobectomy and will be discussed further.

Thy 4: In this category is included cytology which is suspicious but not diagnostic of non-follicular carcinoma. The material from the aspirate should be used for immunocytochemistry to confirm medullary carcinoma or flowcytometry to confirm lymphoma.

Thy 5: In this category the cytology is diagnostic of malignancy.

The American Thyroid Association (ATA) recommends FNAC for nodules > 1cm in patients without risk factors for thyroid cancer whether palpable or not. In patients with risk factors for thyroid cancer (e.g., childhood head and neck irradiation, family history of thyroid cancer) and or presence of highly suspicious characteristics on ultrasound, the ATA guidelines suggest that the nodule threshold size for FNAC is smaller.

Core biopsy - Hahn et al. studied a total of 88 patients who underwent ultrasound-guided Core Needle Biopsy in view of inconclusive FNAC results and concluded that though core biopsy is useful for diagnosis of lymphoma, it's not beneficial for diagnosis of follicular neoplasm (19).

Nodules larger than 4 cm and cystic nodules

In a consecutive series of 361 patients and 382 nodules larger than 4 cm on pre-operative ultrasound, the rate of clinically significant thyroid cancer was found to be 22%. Thyroid cancer was found in 20% of the 86 nodules that were benign on ultrasound. The cancer rate was 10.4% for cytological benign nodules, 29.6 % for cytologically indeterminate nodules and 100% for cytologically malignant nodules. The false negative rate of benign cytology found to be 10.4%. The authors concluded that in nodules larger than 4 cm, neither the absence of suspicious features on ultrasound nor a benign cytology reliably excludes malignancy and should therefore be considered for diagnostic lobectomy (20).

In a retrospective study of 221 surgically resected thyroid nodules, there were 71 (32%) cystic nodules of which 14% had malignancy and 150 (68%) solid lesions of which 23% had cancer. There were no differences in patient demographics, nodule size or whether they were solitary or not. Thus, cystic nodules are as likely as solid ones to harbour malignancy and FNAC is slightly less reliable when a nodule is fluid-filled. The authors therefore recommended that cysts that recur after aspiration should be considered for surgery (21).

Patients and methods

The Trust Research and Development department deemed this study to be a service evaluation and so advised that we did not need its approval. This was confirmed by the National Research Ethics Service (NRES).

We also had the support of the departments of surgery, radiology and pathology for this project. Our hospital caters to a population of 300,000 people. Patients with thyroid swellings are referred by general practitioners. Patients with suspicion of cancer are seen within two weeks in compliance with the directives of the Department of Health. Another source of referral is thyroid nodules found incidentally on imaging for other purposes such as CT scan, carotid Doppler, PET scans and MRI. Occasionally patients with toxic nodules are referred by endocrinologists to the thyroid surgeons for definitive surgical management. All patients who had fine needle aspiration cytology in the hospital were captured electronically into the cytology database. From this database all patients who had thyroid cytology from July 2006 to July 2011 for a period of 60 months was selected. Patient demographics, cytological grading and final histology if any were entered into Microsoft Excel.

After clinical assessment, the patients are referred for ultrasound. There are two radiologists in the hospital with special interest in thyroid ultrasound. They perform ultrasound guided fine needle aspiration cytology. Usually for nodules more than 1 cm FNAC is performed using local anaesthetic with a 25 gauge needle. While the patient is holding his or her breath the needle is passed and rocked gently under suction with a 10 ml syringe. The aspirate is sprayed on to glass slides, air dried and labelled with patient details. There is no facility in our hospital for immediate analysis of the slides to check for the adequacy of cellular material.

We have a fortnightly multidisciplinary team (MDT) meeting of endocrine physicians, surgeons, radiologists, pathologists and specialist nurses. All patients who have had FNAC are discussed. If there are any Thy 3 or if a second opinion is sought, the slides and images are sent to a teaching hospital so that they can be reviewed in the network specialist MDT meeting. This is a video-linked meeting of two teaching and two district general hospitals. The images and slides are reviewed and the group confirms it is a Thy 3 and recommends a diagnostic lobectomy or downgrades the report to a Thy 2. There is a MDT co-ordinator and specialist nurse to facilitate the pathway. This discussion in a regional cancer network is in compliance with the British Thyroid Association guidelines. Patients have a continuing access to a specialist nurse for guidance and support.

Results

Over a period of 60 months from July 2006 to July 2011, there were 621 patients who underwent fine needle aspiration cytology for thyroid nodules. The age range of the patients was 17 to 99. The mean age was 56.4 years. There were 85 males and 536 females. So, final-

TABLE 1 - THYROID NODULES CLASSIFIED ACCORDING TO CYTOLOGICAL CATEGORIES.

Cytology category	Thy 1	Thy 2	Thy 3	Thy 4	Thy 5
Numbers	269 (43%)	287 (46%)	48 (7.7%)	11 (1.7%)	6 (0.96%)

TABLE 2 - PROPORTION OF PATIENTS WITH CANCERS ACCORDING TO CYTOLOGICAL CATEGORIES.

Cytology category	Thy 1	Thy 2	Thy 3	Thy 4	Thy 5
Proportion of cancers	5 (1.8%)	4 (1.3%)	12 (25%)	9 (81%)	5 (100%)

ly there were 269 patients with Thy 1(43%), 287 with Thy 2(46%), 48 with Thy 3(9%), 11 with Thy 4(1.7%) and 6 had Thy 5(0.96%) (Table 1). There were a total of 35 cancers of which 12 were in the Thy 3 category. The break-up of the cancers in the Thy 3 category were- 7 papillary, one lymphoma, one of each of follicular, Hurthle cell, anaplastic and medullary thyroid cancer. The proportions of cancers according to cytological categories are: Thy 1(1.8%), Thy 2(1.3%), Thy 3(25%), Thy 4 (81%) and Thy 5(100%) (Table 2). All the cancers in the Thy 1 and Thy 2 categories were incidental micropapillary carcinomas.

Discussion

The present study shows that about a third of all the cancers were detected in nodules with Thy 3 cytology and also 25% of nodules in this group (Thy 3) had cancer. We compared our results to the fourth National Audit report of the British Association of Endocrine and Thyroid surgeons (BAETS) audit and other studies. The rates of malignancy according to cytological category were-Thy 5-98%, Thy 4 63%, Thy 3- 21%, Thy 2- 7.1% and Thy 1-11.5% (22). The rates of thyroid cancer in the Thy 3 category in our study are similar to the above audit. The findings in our study should be tempered by fact that our study was observational and retrospective. The current management of offering diagnostic lobectomy to patients with Thy 3 cytology has its drawbacks. A quarter of patients with Thy 3 would undergo a re-operation i.e. completion thyroidectomy a few weeks after the diagnostic lobectomy when the fibrosis would be intense and thereby increase the surgical risk especially that of recurrent laryngeal nerve injury. By the same extension, three fourths of the patients would have had a surgical procedure for benign disease and been exposed to the risk of surgery. In view of the current unsatisfactory management of thyroid nodules with Thy 3 cytology, serious attempts are being made to improve the pre-operative diagnosis of Thy 3 cytology. Nodules with Thy 5 would proceed to total thyroidectomy and lymph node dissection. Patients with Thy 4 cytology

would have total thyroidectomy and also be discussed in the MDT focussing on the clinical, pathologic and radiological characteristics to decide whether they would benefit from lymph node dissection.

Many authors have sub-classified the Thy 3 category to improve diagnostic accuracy though in our study it was not performed. In a study of 1150 consecutive thyroid fine needle aspiration specimens by Pagni et al., it was found that atypical proliferations were more often malignant than either follicular or Hurthle cell lesions (23). In a similar study by Deandrea et al., further classifying the Thy 3 lesions improved diagnostic accuracy. The proportions of cancers in each group were Thy 3a ("follicular lesions of indeterminate significance"), Thy 3b ("follicular neoplasm") and Thy 3c ("Hurthle-cell neoplasm") 4.95%, 25.0% and 22.77% respectively (24). Various modalities are being tried to improve the diagnostic accuracy in Thy 3 nodules and reduce the rates of diagnostic lobectomy - for example PET scan, molecular markers, oncogene detection, and ultrasound elastography. Recently, 18FDG-PET scanning has been applied to identify indeterminate nodules that are malignant, but is not sufficiently accurate for routine use although the risk of malignancy in nodules found incidentally on 18FDG-PET scanning could be as high as 27% necessitating immediate attention (25).

Recently, large prospective studies have shown that genetic and protein markers (example-galectin-3) are promising in improving preoperative diagnostic accuracy for patients with indeterminate thyroid nodules. Many of these markers are available for commercial use in reference laboratories have not yet been widely applied in clinical practice. It is likely that some or combination of molecular markers will be used in the future to optimize management of patients with indeterminate cytology. Those being developed have shown promise but are not sufficiently sensitive or specific for routine use (26).

In a study of 265 indeterminate nodules by Alexander et al. using gene expression classifiers, a negative predictive value of 95% was found for follicular neoplasm. They concluded that in cytologically indeterminate nodules with benign gene-expression classifier results, a con-

servative approach can be adopted (27). In a study of 265 indeterminate nodules (85 of which were malignant), using mRNA expression analysis and a gene expression classifier were trained on FNA samples to detect benign thyroid nodules. The classifier had a negative predictive value for malignancy of 95 and 94 percent for samples showing follicular lesion/atypia of undetermined significance and follicular neoplasm, respectively. It is suggested that application of this classifier would save over 60 percent of patients from diagnostic thyroid surgery (28). In a study by Bartolazzi et al., Galectin-3-expression analysis was carried out on 465 thyroid nodules preoperatively and its diagnostic accuracy was determined by comparing this with the final histopathology. Despite a negative predictive value of 91%, this modality missed 22% of cancers (29).

Ultrasound elastography measures the Strain index (SI) which is the ratio of the nodule strain divided by

the strain of the softest part of the surrounding normal tissue and a $SI \geq 2.905$ conferred to the nodule a significantly greater probability of being malignant (30).

Conclusion

So, at the present time, though sub classification of Thy 3 lesions improves diagnostic accuracy, the only way to resolve with certainty whether a indeterminate thyroid nodule is benign or malignant is by performing a diagnostic lobectomy. However, most patients (75 percent) undergo surgery for what is ultimately confirmed to be benign disease. Hopefully in the future one or more of the technologies discussed above would become robust enough to improve the accuracy of pre-operative diagnosis and thereby change this practice.

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