Thy 3F and 3a malignancy rate, a multisite regional retrospective case series

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ABSTRACT

INTRODUCTION The aim of this study was to ascertain the incidence of thyroid cancer for patients categorised as Thy3, 3a or 3f across four tertiary thyroid multidisciplinary centres in the UK.

MATERIAL AND METHODS This is a retrospective case series examining patients who presented with a thyroid nodule and diagnosed as Thy3, 3a or 3f according to the Royal College of Pathologists modified British Thyroid Association and Royal College of Physicians Thy system.

RESULTS In total, 395 patients were included in this study. Of these, 136 turned out to have benign thyroid disease and 24 had micropapillary thyroid carcinomas. The overall rate of thyroid malignancy was 28.8%. For each subcategory, the rate of malignancy was Thy3 24.7%, Thy3a 30.4% and Thy3f 29.2. However, the incidence of thyroid malignancy varied considerably between the four centres (Thy 3f 18–54%).

DISCUSSION The diagnosis of thyroid cancer is evolving but detection for malignancy for indeterminate nodules remains below 50% for most centres around the world. In 2014, the British Thyroid Association subdivided the original Thy3 category into Thy3a and Thy3f and recommended a more conservative approach to management for Thy3a nodules. Despite this, only two centres yielded a higher conversion rate of malignancy in the new higher graded Thy3f group compared with Thy3a.

CONCLUSION It is debateable whether the new ‘Thy3’ subcategories are more useful than the original. Local thyroid malignancy rates may also be more useful than national averages to inform treatment decisions.

KEYWORDS

Thyroid – Malignancy – Fine-needle aspiration – Thy – Ultrasound

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Introduction

The incidence of thyroid cancer in the UK has risen by 149% since the 1970s,¹ but this disease still makes up less than 1% of all cancers treated in the UK. This is mirrored by statistics from the British Association of Endocrine and Thyroid Surgeons audit in 2012, which highlighted that over 50% of all thyroid surgery carried out in the UK was for benign disease.² The standard diagnostic method for managing a thyroid nodule is by ultrasound-guided fine-needle aspiration. The Royal College of Pathologists (RCPATH) has produced updated guidance on thyroid cytological reporting in 2016, with expected positive predictive value for malignancy with each cytological category.³ In the UK, cytological examination is graded from Thy1–5 in accordance to the Royal College of Pathologists modified British Thyroid Association

(BTA) and Royal College of Physicians ‘Thy’ system.^{3,4} Thy3 represents the most challenging diagnosis from a histological point of view because this could represent a benign follicular adenoma, hyperplastic nodule, or alternatively, follicular carcinoma or follicular variant papillary thyroid carcinoma. To elicit a precise diagnosis, hemithyroidectomy is often recommended but this has associated operative risks.⁵ The current BTA guidelines published in 2014 recommend a different approach to management of Thy3f and Thy3a nodules: repeat investigation by further ultrasound assessment with or without repeat fine-needle aspiration for Thy3a nodules and diagnostic hemithyroidectomy for Thy3f specimens.⁵ For patients, understanding the ambiguity around Thy3 nodules and the underlying risk of thyroid cancer can be challenging. Therefore, preoperative patient counselling is key to help patients understand the risks and

benefits of diagnostic thyroid surgery. The aim of this study was to establish the risk of thyroid cancer for the two new Thy3 subcategories across four tertiary thyroid multidisciplinary team units.

Materials and methods

This was a multicentre retrospective case series examining patients undergoing cytological investigation for thyroid nodules. From January 2014 to January 2016, all fine-needle aspiration results were examined for every patient who underwent investigation of a thyroid nodule at the following NHS trusts: Brighton and Sussex University Hospitals, East Kent Hospitals University NHS Foundation Trust, Medway NHS Foundation Trust and Royal Surrey County Hospital NHS Foundation Trust. Patients with a Thy3, Thy3a or Thy3f cytology were identified using cytology reports, multidisciplinary team discussion reports and operating databases. The cytology results were then compared with the final histopathological results to determine the risk of thyroid cancer.

This was a retrospective audit of clinical practice with no change in intervention, ethical committee approval was therefore not required.

Results

In total, 395 patients had a fine-needle aspiration indicating a Thy3, Thy3a or Thy3f lesion. Of these, 30 patients did not progress to thyroid surgery and did not have any formal histopathology recorded against their details. Four of these patients died, within the same year that the fine-needle aspiration was taken, from an unrelated illness and one was deemed unfit for surgery. Two histopathology results were still pending and twenty patients with Thy3a nodules were awaiting further investigations which had not been completed at the end of the study period. Despite examination of the multidisciplinary team outcome documentation and communication directly with pathology departments, it remained unclear why the remaining three patients did not complete a form of treatment.

The study captured a period of transition as each department switched to the 2014 guidelines, Royal Surrey had no Thy3 specimens, Medway had one (less than 1%), Brighton 26 (52%) and East Kent 50 (37%).

The mean age of all patients was 51 years, with a range from 6 to 88 years. The total rate of malignancy was 28.8% excluding microcarcinomas of which there were 24 (6.6%; 23 of which were micropapillary and 1 microfollicular). The conversion from Thy3 to malignancy was 24.7%, Thy3a 30.4% and Thy3f 29.2%. The frequency of papillary thyroid cancer was equal to follicular cancer (45 patients each). The frequency of each cancer subtype and the conversion of malignancy for each Thy grade for each individual site is shown in Figures 1 and 2.

Discussion

In 2014, the BTA issued new guidelines on the management of thyroid cancer. Thyroid cytology is now divided into seven different categories rather than the traditional five based on fine-needle aspiration cytology. These categories are: Thy1 (non-diagnostic sample), Thy2 (normal thyroid tissue, colloid nodule, thyroiditis), Thy2c (cystic sample containing abundant amounts of colloid tissue), Thy3a (degree of atypical features, but not enough features to upgrade to a higher level of suspicion), Thy3f (where follicular neoplasm is suspected but cannot be excluded on cytology alone), Thy 4 (suspicious of malignancy), Thy5 (definite malignant tissue). For Thy3a cytology, further assessment is recommended and discussion with the local multidisciplinary team, often recommending repeat ultrasound and fine-needle aspiration at a later date.³ The last national UK audit found that only 21.5% of patients with a Thy3 grading on fine-needle aspiration had thyroid cancer.⁶ In this study, the rate of malignancy was not higher in the Thy3f group compared with Thy3 or Thy3a. Worldwide the rate of malignancy for indeterminate specimens ranges from 17.5% to 43%.^{7–14} Diagnosing benign compared with malignant follicular neoplasm is problematic because of the need to examine for the presence of capsular or vascular invasion, which is why a formal histological specimen is often necessary.¹⁵ Therefore, a large proportion of patients may be undergoing unnecessary thyroid surgery because a superior method for detecting thyroid cancer does not currently exist.

Examining thyroid nodules with ultrasound has become common practice and the evidence suggests that certain radiological features are associated with malignant thyroid nodules: hypoechogenicity, microcalcifications and irregular borders. The association of each feature with malignancy varies in the literature between 23.9% and 93%,^{16–18} therefore deciding which feature to use as a marker of malignancy poses difficulties. The BTA in 2014 recommended the adoption of an ultrasound grading system of U1–U5 to stratify risk of thyroid cancer based on groupings of radiological features.⁵ This is similar to the thyroid imaging reporting and data (TIRAD) system, which was promoted by the Horvath group in America in 2009 and has been reported to have a sensitivity of 0.79 and specificity of 0.71 for the ability to differentiate between the different types of thyroid nodules.^{19,20} The Horvath group reports that a TIRAD score of 1 or 2 is associated with a low risk of malignancy (0–1.79%) but did originally report a large variation in the reported malignancy rate for TIRAD 4 (5–95%). Kwak *et al.*²¹ then subdivided this into 4A and 4B and the Horvath group suggested adding in 4C, as subdividing this category appears to improve the diagnostic yield of thyroid malignancy (4A 5.88%, 4B 62.82 %, 4C 91.22%).²² This subdivision is not currently part of the UK thyroid ultrasound classification system. Features on ultrasound were examined during the

data collection period in this case series. Unfortunately, the features documented in radiological reports were sporadic and the use of the U grading system only just started to

appear in some of the reports at the end of 2015. As subspecialisation and thyroid specific expertise within radiology departments increases, reporting standardisation may also

Figure 2 Percentage of benign and malignant lesions per thy grading by individual NHS hospital trust (thyroid microcarinomas are excluded)

improve along with reliable use of the U grading system to aid clinical decision making.

The diagnosis of thyroid cancer is evolving but detection for malignancy for indeterminate nodules remains below 50% for most centres around the world. A large number of patients are still potentially undergoing hemithyroidectomy for often asymptomatic benign disease. Hemithyroidectomy carries significant risks of postoperative morbidity, so it is therefore essential that patients are provided with the right information regarding their risk of thyroid cancer because for every patient their level of acceptable risk will differ based on their own experiences and beliefs. It is clear from the results that local rates of malignancy for the Thy3, Thy3a and Thy3f categories vary considerably.

The introduction of the Thy3a group has resulted in an increased burden on radiology departments with regard to ultrasound provision. In all four centres, patients presenting with Thy3a cytology in the absence of significant risk factors will undergo a second ultrasound scan at an interval of 3–6 months with repeat fine-needle aspiration, as evidence shows that up to 70% of patients are reclassified at repeat biopsy.²⁵ If at this time cytology is once again Thy3a and the U grading is 3 or above, the multidisciplinary team general consensus would be to suggest that a hemithyroidectomy is discussed with the patient. If a patient were to decline surgery, then surveillance ultrasound at six-monthly intervals would potentially be offered to ensure that malignant disease is not missed for a period of 24 months. If the U grading is 4 or above but the cytology is Thy2 then a core biopsy would be considered at the multidisciplinary team meeting. Subsequently, if diagnostic uncertainty still remains this subgroup would also then be offered a hemithyroidectomy. All multidisciplinary team members are in agreement that for indeterminate thyroid cytology, the patient's wishes and individual cancer risk profile play a significant role in the decision-making process.

The experience of the histopathologist also plays an important role in indeterminate disease. Studies have shown that the opinions of histopathology specialists regarding specific cytological subtypes can vary from 8 to 13%.²⁴ In one centre, review of discordant histology by a senior pathologist (greater than four years' experience) resulted in an improved malignancy rate from 17.7% to 27.7%.²⁵ Perhaps a national centre for cytological analysis could be one way to improve accuracy. Interobserver variability may explain differences in Thy3a and Thy3f rates across the four centres studied. There were between three and six reporting cytopathologists at each site, the majority of whom did not have a subspecialist interest in thyroid. In particular, Medway and Brighton had the most, five and six respectively, reporting thyroid fine-needle aspiration specimens. At Royal Surrey, there were three reporting cytopathologists with the majority reported by one senior pathologist. This changed midway through the study, owing to retirement, after which all samples were graded and then sent to the Royal Marsden Hospital for review. East Kent has five reporting pathologists.

It is also worth considering whether local malignant conversion rates should be used to inform patients being considered for hemithyroidectomy rather than international or

national averages. Differences in local rates may be reflect the local populace as certain geographical areas may contain individuals with a proportionately higher or lower collection of risk factors known to be associated with thyroid cancer. Regional variations in dietary iodine insufficiency may also play a part.²⁶ It would be interesting to see what the degree of variation is around the UK nationally and this type of publication may highlight the need to examine outlying regions in further detail. High-detection centres may either have an exceptional practice that could help develop new models of care or be a reflection of problems within a centre's diagnostic pathway.

In conclusion, this is one of the first studies examining the impact of the changes to the Thy3 category introduced into the UK during 2014. Only two centres yielded a higher conversion rate of malignancy in the new higher graded Thy3f group compared with Thy3a. It is therefore debatable whether the Thy3a and Thy3f subcategories are more useful than the original Thy3 category and another UK national audit would be a useful tool to aid this debate.

There is also large geographical variation in thyroid cancer detection rates for these indeterminate nodules. Perhaps clinicians should be using local conversion rates to council patients as part of the informed consent process for deciding between a diagnostic hemithyroidectomy or active monitoring with serial ultrasound and cytological assessment. Future work needs to be completed to examine national variations and to analyse the impact and effectiveness of the new U grading system.

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