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Risk of malignancy in Thy3 thyroid nodules

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Objective. Thyroid cancer is the most common endocrine malignancy in humans. Ultrasound guided fine needle aspiration cytology (FNAC) is now considered the best diagnostic tool for the evaluation of any thyroid nodule. Thyroid cytology is graded from Thy1 to Thy5 with Thy3 being the most challenging in diagnosis. Our aim was to identify the risk of malignancy in Thy3 cytology in our centre. This risk should be explained to the patient before taking any decision.

Methods. One hundred and one patients were included in our study. All patients had Thy3 cytology on preoperative ultrasound scan guided FNAC. All patients had diagnostic hemithyroidectomy. The results from the histology were compared with the cytology findings and the rates of malignancy were identified.

Results. Of the 101 patients, 17 were males and 84 females. Average age for diagnosis was 52.4±15 years of age. Patients were classified into three groups; patient who had completely benign histology (n=70), patients who had incidental finding of micro-carcinoma after diagnostic hemithyroidectomy (n=10), and patients who had thyroid macro-carcinomas (n=21). Total rate of malignancy was 30.7% when combining both the malignant and the incidental groups and 20.8% when excluding the incidental group.

Conclusion. Our rates of malignancy in Thy3 cytology are similar to the literature. These rates should be explained clearly to the patient during the preoperative counselling. Future advances in biomarkers technology may help to improve the preoperative diagnostic accuracy and reduce the rate of unnecessary thyroid surgery.

Keywords: thyroid nodule, Thy3, cytology, histology, cancer rate

Thyroid gland cancer is the most common malignant endocrine tumour in humans despite representing less than 1% of all malignancies treated in the United Kingdom (Cancer Research UK 2022). It is estimated that 4% to 7% of the adults may present a palpable thyroid nodule and up to 70% have thyroid nodule(s) on high-resolution ultrasonography (Guth et al. 2009). Although the majority of these nodules are benign, about 15% of them are malignant (Hadjisavva et al. 2015). Whilst the mortality from thyroid cancer may have decreased significantly in the last 40 years, there are still around 400 deaths per year from thyroid cancer (Cancer Research UK 2022). It has been estimated that more than eight in ten (84.3%) of people diagnosed with thyroid cancer in England would survive their disease for ten years or more (2013–2017) (Cancer Research UK 2022).

Ultrasound guided fine needle aspiration (FNA) is now considered the mainstay of diagnosis for thyroid nodules. In addition, cytological evaluation of FNA has decreased the number of patients undergoing thyroid surgery. However, fine needle aspiration cytology (FNAC) has its own limitation as in 10% to 15% of cases, FNAC may be not diagnostic, i.e., the material is insufficient for diagnosis, and in 5% to 20%, it is not possible to differentiate between benign

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follicular adenoma and carcinoma (Hamburger 1994; Greaves et al. 2000). For FNAC reporting, the Royal College of Pathologists (RCPath) thyroid reporting system was developed by building on the existing British Thyroid Association (BTA) system (6 British Thyroid Association 2014). It was originally issued in 2009 (Cross et al. 2009), and revised in 2016 (Cross et al. 2016). The most widely used system currently in the UK is the BTA/RCPath 'Thy' system, which graded thyroid cytology from Thy1–5. Thy3 represents the most challenging diagnosis because this could represent a benign follicular adenoma, hyperplastic nodule or alternatively, follicular carcinoma or follicular variant papillary thyroid. Studies have shown that 20% to 52% of Thy3 results were malignant (Carling and Udelsman 2005; Cross et al. 2016).

The current 2016 RCPath guidance has divided the indeterminate category 'neoplasm possible-Thy3' into Thy3a (neoplasm possible–atypia/non-diagnostic) and Thy3f (neoplasm possible, suggestive of follicular neoplasm) (Cross et al. 2016). The BTA guidelines recommend a different approach to management of Thy3f and Thy3a nodules: repeat investigation by further ultrasound assessment with or without repeat FNAC for Thy3a nodules and diagnostic hemithyroidectomy for Thy3f cytology (Cross et al. 2016). Hemithyroidectomy is associated with multiple risks (Mijovic et al. 2009). Therefore, preoperative counselling for patients with Thy3 thyroid lesions is very important. The risk of malignancy in addition to the pros and cons of diagnostic thyroid surgery should be discussed thoroughly.

The aim of the current study was to identify the possible risk of thyroid cancer in Thy3 lesion (both Thy3 and Thy3f) in our centre. This risk should be discussed clearly with patients having Thy3 lesions during the stage of decision making.

Table 1
Patients' demographics

Variable	Number
Age (years)	52.4±15.0
Males	17
Rate of malignancy in Thy3 thyroid nodules	
Benign	10
Incidental carcinoma	1
Malignant	6
Females	84
Rate of malignancy in Thy3 thyroid nodules	
Benign	60
Incidental carcinoma	9
Malignant	15
Tumour size (mm)	25.9±16.7
Laterality	
Right	63
Left	38

Patients and Methods

We carried out this retrospective study for patients who were diagnosed with Thy3 lesions on FNAC in our general surgery department during the period from 2018 to 2020. All the data were obtained from the hospital recording system. All our patients were referred to the endocrine surgery services for assessment of thyroid nodules. All patients had clinical and radiological assessment by ultrasonography performed by at least a senior radiologist. Indeterminate and suspicious thyroid nodules on ultrasonography were further evaluated by FNAC. All cases with Thy3 thyroid lesions were discussed in our thyroid multidisciplinary meeting. The risks of malignancy, the advantages and complications of surgery were discussed with all the patients. A written consent was obtained from each patient. Ethical approval was not required as the data included were retrospectively collected, fully anonymized, and not including any biological samples.

Inclusion criteria included (1) patients who had thyroid nodule(s) confirmed as Thy3a or Thy3f on FNAC, (2) patients who had diagnostic hemithyroidectomy following FNAC results, and (3) patients of any age group. Exclusion criteria include (1) other FNAC results than Thy3, (2) patients with known metastatic thyroid cancer, (3) benign thyroid pathology, and (4) patients who did not have any diagnostic thyroid surgery. The results from the FNA were compared with the final histology results obtained from diagnostic hemithyroidectomy. The risk of malignancy was identified for both groups, Thy3a and Thy3f.

Results

During the period from 2018 till 2020, more than 250 thyroid surgeries were carried out in our general surgery department. One hundred and one patients were eligible for our study according to the inclusion and exclusion criteria. Average age at diagnosis was 52.4±15.0 years. Average size of the nodules on histology was 25.9±16.7 mm. Seventeen of the patients

were males and 84 females. Of the 17 males, ten were found to have benign thyroid nodules, six had cancer, and incidental carcinoma was found in one patient. Of the 84 females, 60 had benign nodules, 15 had malignancy, and incidental carcinoma was found in nine patients (Table 1).

All the 101 patients had an initial assessment by ultrasonography guided FNAC (Figures 1–4). Eighty-eight patients had U3 nodules and 13 had U4. Of the 88 patients with U3 nodules, 64 had benign thyroid lesion, 16 had thyroid cancer, and 8 incidental finding of thyroid cancer. On the other hand, of the 13 patients with U4 nodules, five had thyroid cancer, six benign thyroid lesions and two incidental finding of thyroid micro-carcinoma (Table 2).

Of the 101 patients, 70 patients had benign nodules, 10 patients had benign nodules with an incidental finding of micro-carcinoma, and 21 patients had macro-carcinomas. Follicular adenoma was the most common benign diagnosis, while follicular carcinoma and follicular variant of papillary thyroid carcinoma were the most common malignancies. In generally, the rate of incidence of malignancy in Thy3 cytology was 30.7% when combining both the malignant and incidental groups, and 20.8% when including the malignant group only without the incidental group (Table 3).

Thirty-eight patients had left hemithyroidectomy, while 63 had right hemithyroidectomy. All patients with confirmed macro-carcinoma had completion hemithyroidectomy. Only one of the patients with an incidental finding of micro-papillary carcinoma had completion hemithyroidectomy with the original nodule was diagnosed as non-invasive follicular thyroid tumour with papillary-like nuclear features (NIFTP).

Table 2
Histology findings according to the British Thyroid Association (BTA) ultrasound (U) classification

Histology findings	U4 (n=13)	U3 (n=88)
Benign	6	64
Incidental carcinoma	2	8
Malignant	2	16

Table 3
Final histology findings after diagnostic hemithyroidectomy

Histology	Number
Entirely benign (total)	70
Goitre/ colloid nodule	21
Follicular adenoma	27
Hürthle cell adenoma	9
Hyperplastic nodule	11
Thyroiditis	1
Cyst	1
Benign with incidental carcinoma (total)	10
Follicular adenoma	5
Hürthle cell adenoma	1
NIFTP	1
Hyperplastic nodule	1
Thyroiditis	2
Papillary micro-carcinoma	7
FVPTC	3
Malignant (total)	21
FVPTC	6
Papillary carcinoma	5
Follicular carcinoma	6
Hürthle cell carcinoma	2
Anaplastic/poorly differentiated carcinoma	2

Abbreviations: FVPTC – follicular variant of papillary thyroid carcinoma; NIFTP – non-invasive follicular thyroid tumour with papillary-like nuclear features.

Table 4
Incidence of malignancy in Thy3a and Thy3f cytology

Malignancy	Thy3a (7 cases)	Thy3f (94 cases)
Benign	4 (57%)	70 (70.2%)
Incidental carcinoma	0 (0%)	10 (10.6%)
Malignant nodule	3 (43%)	18 (19.0%)

Discussion

Thyroid cancer is the 20th most common cancer in the UK, accounting for 1% of all new cancer cases between 2016 and 2018 (Cancer Research UK 2022). About 40% of the general population have single or multiple thyroid nodules (Mihai et al. 2009). It is estimated that 5% to 10% of all thyroid nodules are malignant (Bhattacharyya and Fried 2002), and 20% to 52% of Thy3 results are malignant. It has been reported that 72% of thyroid cancer cases in the UK are in females, and 28% are in males (Cancer Research UK 2022). We had similar results with female to male ratio of about 3.4:1.0. In addition, the peak age of diagnosis of thyroid cancer in the UK between 2016 and 2018 was in people aged 65 to 69 (Cancer Research UK 2022). The average age of diagnosis in our study was 52.4±15.0 years.

Ultrasound scan is a highly sensitive non-invasive and cost-effective technique for assessment of thyroid nodules (Kelley 2011; Baloch et al. 2008)

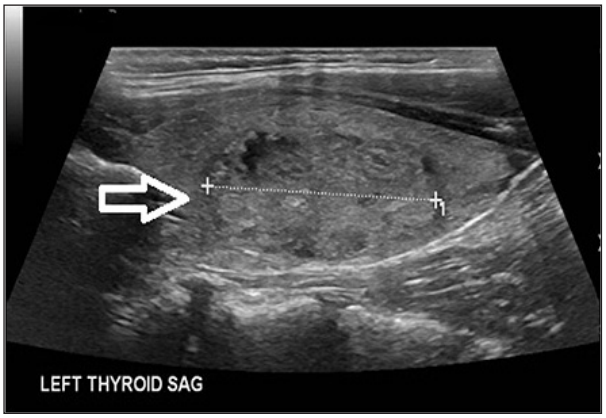


Figure 1. The neck ultrasound scan showing an 18×14×30 mm U3 well-defined isoechoic nodule (arrow) within the left thyroid lobe containing small cystic components with peripheral and central vascularity, Thy3f on fine needle aspiration cytology (FNAC). Final histology confirmed the hyperplastic changes.

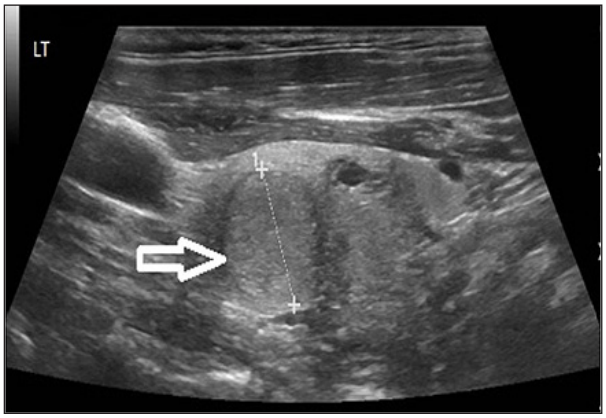


Figure 2. The neck ultrasound scan showing an iso to hyperechoic U3 left thyroid nodule (arrow) with a thin surrounding halo and internal and peripheral vascularity measuring 1.5×1.3×1.1 cm, Thy3f on fine needle aspiration cytology (FNAC). Final histology confirmed the Hurtle cell adenoma.

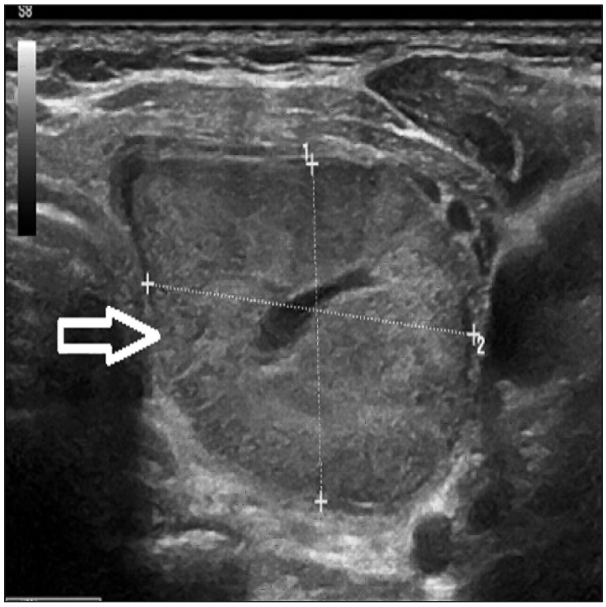


Figure 3. The neck ultrasound scan showing a 17×26 mm indeterminate U3 nodule (arrow) identified in the left lobe of the thyroid gland with prominent blood flow on colour Doppler, Thy3f on fine needle aspiration cytology (FNAC). Final histology confirmed the follicular carcinoma.

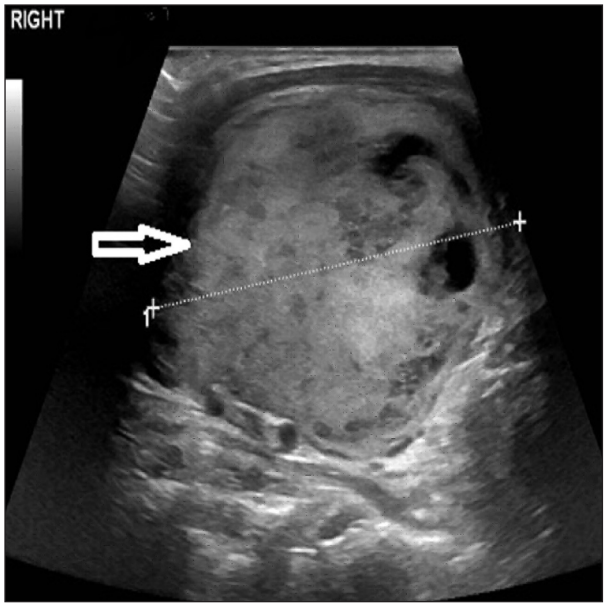


Figure 4. The neck ultrasound scan showing an indeterminate U3 right thyroid nodule (arrow) measuring up to 6.5 cm. The nodule is hyperechoic with occasional areas of spongiform/cystic changes. Final histology confirmed adenomatous hyperplasia with a co-incidental finding of a 2.5 mm papillary microcarcinoma.

and allows targeted ultrasound scan guided FNAC. Although certain radiological features are associated with malignant thyroid nodules: hypoechogenicity, microcalcifications, and irregular borders, no single feature in isolation has sufficient diagnostic accuracy to reliably confirm or exclude malignancy (Russ et al. 2017; Park et al. 2016). Different systems have been used to classify thyroid nodules to safely help to detect all thyroid cancers, while minimising the number of patients undergoing FNA, which is associated with patients' anxiety and increased cost (Brito et al. 2014). Among these systems are the TIRADS (Horvath et al. 2009; Remonti et al. 2015), EU-TIRADS (Baloch et al. 2008; Russ et al. 2017), and the BTA ultrasound (U) classification (Brito et al. 2014). The BTA ultrasound classification has categorised

thyroid nodules into five categories, U1 to U5, based on features including echogenicity, contour, halo, colloid artefact, calcification and vascularity (British Thyroid Association 2014; Kanona et al. 2017). U1 represents normal thyroid parenchyma, U2 a benign nodule, U3 an indeterminate/equivocal nodule, U4 a suspicious nodule, and U5 a malignant nodule. FNAC is recommended for nodules classified as U3 or above (Brito et al. 2014; Perros et al. 2014). Of our patients, 88 had U3 nodules and 13 had U4. On the final histology, of the 88 patients with U3 nodules, 64 had benign thyroid lesion, 16 had thyroid cancer and eight had incidental finding of thyroid cancer while the nodules of concern were confirmed to be a benign nodule. On the other hand, of the 13 patients with U4 nodules, five had thyroid cancer, six had benign thyroid lesions and two had incidental finding of thyroid carcinoma (Figures 1–4).

The UK 'Thy' terminology was developed for reporting thyroid FNAC, to guide management of the thyroid nodule. In 2002, the national guidance from the BTA and the Royal College of Physicians of London was introduced for the management of thyroid cancer in adults (Royal College of Physicians 2002), followed by a second edition in 2007 (British Thyroid Association and Royal College of Physicians 2007), and a third edition in 2014 (British Thyroid Association 2014). In 2009, the UK RCPath published the first edition of the 'Thy' terminology (Cross et al. 2009), which was revised in 2016 (Cross et al. 2016). The current 2016 RCPath guidance has divided thyroid cytology into seven different categories rather than the traditional five, based on FNAC. These categories are: Thy1 (non-diagnostic sample), Thy2 (normal thyroid tissue, colloid nodule, and 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), Thy4 (suspicious of malignancy), Thy5 (definite malignant tissue). It was reported that Thy3 results account for around 9% of FNA results from the thyroid (Carling and Udelsman 2005).

The differentiation between follicular adenoma and carcinoma is usually challenging because it depends mainly on capsular or vascular invasion, which is difficult to be obtained with FNAC only. That is why a large proportion of patients may undergo unnecessary thyroid surgery (Greaves et al. 2000). Literature review shows that between 20% and 52% of Thy3 results are malignant (Carling and Udelsman 2005; Cross et al. 2016). Moreover, according to the RCPath 2016, the malignancy rate for Thy3a cytology ranges from 5% to 15%, and for Thy3f ranges from 15% to 30% (Cross et al. 2016). In our study, 101 patients were diagnosed with Thy3 cytology on preoperative FNA. All the patients had diagnostic hemithyroidectomy. 70 patients (69.3%) were found to have benign thyroid nodule(s), 21 (20.8%) had thyroid carcinoma and in ten patients (9.9%) there was an incidental finding of thyroid micro- carcinoma, where the nodule(s) of concern itself was confirmed to be benign in nature. The incidence of incidental thyroid cancer was found to range from three to 16% in different series (Nanjappa et al. 2013). Three out of the seven patients, who had Thy3a cytology, had thyroid malignancy. On the other hand, of the 94 patients who had Thy3f cytology, 66 had benign histology, 18 had thyroid malignancy and incidental micro-carcinomas were found in ten (Table 4). We found that the most common malignancies were the follicular carcinomas (FTC) (n=6) and follicular variant of papillary thyroid carcinoma (FV-PCT) (n=6). Studies reported that follicular variant of papillary thyroid carcinoma (FV-PTC) is the most common subtype of papillary thyroid carcinoma (PTC) (Yu et al. 2013). It was reported also that the 10-year disease-specific survival for patients with FV-PTC was 98%, classical PTC was 97%, and for FTC was 94% (Yu et al. 2013). The two main types of micro-carcinoma, which were incidentally found are papillary thyroid carcinoma (n=7) and follicular variant of papillary thyroid carcinoma (FV-PCT) (n=3). On the other hand, follicular adenoma was the most common benign diagnosis in our study (n=27). This can explain the limitation of FNAC in the differentiation between follicular benign and malignant pathology.

For Thy3a cytology, multidisciplinary team discussions, patient's wishes plus or minus repeated FNAC have been the keystones in management. While for Thy3f cytology, diagnostic hemithyroidectomy has been usually recommended. Diagnostic hemithyroidectomy has been associated with lots of morbidities including recurrent laryngeal nerve injury (voice change), bleeding, infection, excessive scarring, risk of general anaesthesia, and patient's distress. Therefore, it is essential that patients should be provided with the right information regarding their risk of thyroid cancer and the possible complications of surgery because for every patient their level of acceptance will differ based on their background experiences and beliefs. No major complications were observed in our study. In case of benign histology, no further intervention was required. For

patients with confirmed malignancy, further interventions in the form of completion thyroidectomy followed by adjuvant radioactive iodine ablation were recommended. While for patients with incidental finding of micro-carcinoma, the majority of patients with favourable histology, had active surveillance with no need for any further intervention (Iniguez-Ariza and Brito 2018), except one patient who had non-invasive follicular thyroid tumour with papillary-like nuclear features (NIFTP) with incidental papillary micro carcinoma, and had completion hemithyroidectomy.

Furthermore, the experience of the histopathologist can play an important role in the diagnosis and interpretation of indeterminate thyroid nodules. Wang et al. (2011) have shown that the opinions of histopathologists regarding the interpretation of certain cytological subtypes can vary from 8% to 13%. In one centre, review of histology by a senior pathologist has resulted in an increase in the malignancy rate from 17.7% to 27.7% (Bellevicine et al. 2017). Here, the importance of multidisciplinary team discussion and a senior histopathologist review is elicited. Recently, new thyroid cancer biomarkers have been extensively investigated such as Afirma gene expression classifier (GEC) (Liu et al. 2019) and ThyroSeq v3 GC sets (Nikiforov and Baloch 2019). Afirma GEC showed a high sensitivity rate (95.5%) (Liu et al. 2019). However, the cost-benefit ratio has limited the universal use of these markers. In addition, further studies and development would be required for more accurate diagnosis.

Nevertheless, we had some limitations in our study. First, we collected the patients' data retrospectively. Second, the number of included patients was limited. Third, not all the included patients were scanned by the same radiographer, which might contribute to the variability in the results and accuracy of the FNAC (Bellevicine et al. 2017). However, all our cases were discussed in a multidisciplinary team meeting and all the ultrasound scan and FNAC findings were reviewed to minimize the chance of any misinterpretation of the findings.

Conclusion

The rate of malignancy in Thy3 can vary widely between different centres. The rate in our study is similar to that in the literature. Although FNA is considered the standard diagnostic method for thyroid nodules, it still has its own limitations. The main difficulty is in the differentiation between benign and malignant follicular lesions. Patient's counselling, senior pathologist review and multidisciplinary team discussion are crucial prior to decision making. The introduction of new advances such as genetic, molecular and imaging biomarkers could help to improve the preoperative diagnosis of thyroid nodules and to avoid unnecessary thyroid surgery in the future; however, more research and funding would be required.

Conflicts of interest: *Authors declared no conflicts of interest.*

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