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Risk of malignancy in radiologically and cytologically discordant thyroid nodules, based on Thyroid Imaging, Reporting and Data System (TI-RADS) and Bethesda classifications

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Introduction

Thyroid nodules are initially assessed using ultrasonography and the sonographic features of a lesion determine the need for further cytological evaluation with fine-needle aspiration (FNA). Subsequent clinical management depends on the result of the FNA. The American College of Radiology (ACR) Thyroid Imaging, Reporting and Data System (TI-RADS) was developed to standardize the description of the ultrasonographic features of thyroid nodules, to allow reproducible scoring of suspicious characteristics, and to avoid unnecessary FNAs[1]. For example, a TI-RADS 1 (T1) or TI-RADS 2 (T2) nodule has a risk of malignancy of less than 5 per cent, whereas, in the TI-RADS 5 (T5) category, more than 80 per cent of nodules are malignant[2]. Clinical practice guidelines recommend FNA for TI-RADS 4 (T4) or T5 nodules greater than or equal to 1 cm, for TI-RADS 3 (T3) nodules greater than or equal to 1.5 cm, and for T2 nodules greater than or equal to 2 cm[3].

The Bethesda System for Reporting Thyroid Cytopathology is a standardized reporting system that classifies thyroid FNA biopsy results into six categories, each with particular diagnostic implications and an associated risk of malignancy[4]. Within this model, nodules classified as Bethesda II (B2; benign) have an estimated risk of malignancy of 0–3 per cent, whereas nodules classified as Bethesda VI (B6; malignant) are malignant in 97–99 per cent of cases.

The current American Thyroid Association (ATA) guidelines recommend no further management once a nodule has been classified as B2[3]. However, the guidelines also acknowledge the importance of high-risk sonographic features in identifying the patients with potential missed malignancy, with follow-up recommendations determined 'by risk stratification based upon US pattern' (where US stands for ultrasonographic), rather than the B2 cytology result. Several factors contribute to the accuracy of the cytological result, including the adequacy of the sample, the experience of the cytopathologist, and the experience of the radiologist or clinician in ensuring a representative sample of the lesion is taken. This aim of this study was to quantify the risk of malignancy in T5 B2 nodules.

Methods

Methods are described in detail in the *Supplementary materials*. Records of patients who underwent thyroidectomy between 2015 and 2020 for T5 B2 lesions were reviewed. Patients diagnosed after surgery with thyroid cancer were classified according to the ATA risk-stratification system[3].

Results

There were 596 patients with B2 nodules who underwent thyroidectomy between 2015 and 2020 (*Table 1*). A total of 33 patients (6 per cent) had T5 ultrasonographic characteristics and all had undergone an ultrasound-guided biopsy that yielded a B2 result. Among T5 B2 patients, eight (24 per cent) had two B2 FNA biopsies, while the remaining 25 (76 per cent) had a single FNA and proceeded to operative management for an additional indication or at the discretion of the treating surgeon. While compressive symptoms remained the most common reason for resection in this group, a significant proportion (30 per cent) proceeded to surgery based on clinical judgement after review of the imaging characteristics.

Of the 33 T5 B2 nodules, ten (30 per cent) were malignant and 23 (70 per cent) were benign or precancerous according to histopathology. The 10 malignant cases are described in *Table 2* and *Table S1*. These cases consisted of seven papillary thyroid carcinomas, one minimally invasive follicular carcinoma, one minimally invasive Hürthle cell carcinoma, and one poorly differentiated papillary carcinoma. Of note, 8 of the 10 (80 per cent) cases were classified as being intermediate or high risk for

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Table 1 Demographics of a cohort of individuals with cytologically benign (Bethesda II) nodules (for individuals with Thyroid Imaging, Reporting and Data System 5 nodules, for individuals with Thyroid Imaging, Reporting and Data System <5 nodules, and for all individuals)

	TI-RADS 5 Bethesda II (*n* = 33)	TI-RADS <5 Bethesda II (*n* = 563)	Total (*n* = 596)
Sex			
Female	29 (88)	441 (78)	470 (79)
Male	4 (12)	122 (22)	126 (21)
Age (years), mean (range)	58.5 (29–85)	56 (17–90)	56.2 (17–90)
Indication(s) for procedure			
Compression	19 (58)	431 (77)	450 (76)
Growth	0	7 (1)	7 (1.2)
Risk of malignancy	10 (30)	68 (12)	78 (13)
Single nodule (non-toxic)	0	4 (0.7)	4 (0.7)
Multi-nodular goitre (non-toxic)	0	5 (0.9)	5 (0.8)
Retrosternal goitre	6 (18)	69 (12)	75 (13)
Single nodule (toxic)	0	2 (0.4)	2 (0.3)
Multi-nodular goitre (toxic)	1 (3.0)	25 (4.4)	26 (4.4)
Graves' disease	0	4 (0.7)	4 (0.7)
Other	0	10 (1.8)	10 (1.7)
Procedure performed			
Total thyroidectomy	14 (44)	223 (40)	237 (40)
Hemithyroidectomy	19 (58)	325 (58)	344 (58)
Nodulectomy	0	6 (1.1)	6 (1)
Other	0	9 (1.5)	9 (1.5)
Histopathology			
Benign	22 (67)	556 (99)	578 (97)
Malignant	11 (33)	7 (1.2)	18 (3.0)

Values are *n* (%) unless otherwise indicated. TI-RADS, Thyroid Imaging, Reporting and Data System.

Table 2 Final histopathology for individuals with Thyroid Imaging, Reporting and Data System 5 Bethesda II nodules; *n*=33

Malignant	10 (30)
Papillary thyroid carcinoma	7
Classical	4
Follicular variant	2
Mixed papillary/follicular	1
Minimally invasive follicular carcinoma	1
Hürthle cell carcinoma	1
Poorly differentiated thyroid carcinoma	1
Benign or precancerous	23 (70)
Single dominant nodule	7
Toxic multi-nodular goitre	2
Non-toxic multi-nodular goitre	10
Riedel's thyroiditis	1
Follicular adenoma	1
Hürthle cell adenoma	1
NIFTP	1
Incidental findings*	
Papillary microcarcinoma	3
C-cell hyperplasia	1

Values are *n* (%) unless otherwise indicated. *Within the 'benign or precancerous' subset of cases. NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features.

structural recurrence according to the ATA guidelines[3]. Pre-malignant lesions consisted of one non-invasive follicular thyroid neoplasm with papillary-like nuclear features, one instance of C-cell hyperplasia, and one Hürthle cell adenoma. A total of six of the eight patients who had two B2 FNA biopsies were found to have benign lesions, while two were ultimately diagnosed as having malignant lesions (one papillary thyroid carcinoma and one minimally invasive follicular carcinoma).

Discussion

This study examines a cohort of individuals who underwent thyroidectomy for radiologically suspicious (T5) but cytologically benign (B2) 'discordant' nodules. Overall, 30 per cent of T5 B2 nodules were malignant and 24 per cent were intermediate or high risk according to the ATA. These rates are higher than expected, based on the false-negative rate associated with the Bethesda scoring system, and suggest clinicians should interpret benign cytology results with caution when the pre-test probability of malignancy is high[5].

Overall, the B2 FNA diagnosis carries a 0–3 per cent false-negative rate[4] and hence the test has an excellent negative predictive value for malignancy, provided adequate sampling occurs. Current guidelines recommend no further management for nodules classified as B2 using cytopathology, regardless of their initial imaging characteristics[3]. The present study demonstrates that the negative predictive value for malignancy of a B2 biopsy drops from 99 to 67 per cent in the presence of highly suspicious imaging features and therefore the management algorithm for the T5 B2 lesion should be informed by the T5 imaging characteristics, rather than the biopsy result. This approach is supported by the fact that 24 per cent of T5 B2 nodules were intermediate- or high-risk malignancies according to the ATA risk-stratification system and hence required additional management after initial surgery (*Table S1*).

There is a paucity of published data describing the management of 'discordant' thyroid nodules. Previous studies have based the diagnosis of malignancy on a combination of serial imaging, FNA biopsy, and surgery, and report rates of malignancy of 3–4.8 per cent[6,7]. Because of the heterogeneity in study design and management algorithms, the rate of malignancy may be underestimated. In addition, there are discrepancies between different ultrasound-based risk-stratification systems, which will influence the interpretation of the published data. For example, although the ACR TI-RADS system, the Kwak TI-RADS system[8], and the ATA ultrasonographic risk-stratification system[3] use similar ultrasonographic features, the scoring systems and risk categorizations differ. For example, all Kwak T5 nodules would be considered ACR T5 nodules; however, a proportion of ACR T5 nodules would not have all five suspicious features and would therefore be classified as Kwak T4 nodules. Using the Kwak TI-RADS classification system, Moon *et al.*[9] report a 22 per cent rate of malignancy in T5 B2 nodules, which is comparable to the results of the present study.

Another important consideration in the pre-test probability of malignancy is nodule size. Wharry *et al.*[10] demonstrate that, among nodules greater than or equal to 4 cm, the risk of malignancy is 20 per cent for nodules with no suspicious sonographic features and 10.4 per cent for cytologically benign nodules, indicating that, in nodules greater than or equal to 4 cm, neither ultrasonography nor cytology reliably exclude malignancy. In the present study, 6 of the 10 (60 per cent) T5 B2 lesions that were greater than or equal to 4 cm were malignant; however, only four of the 149 (2.7 per cent) nodules that were greater than or equal to 4 cm in the TI-RADS less than TIRADS 5, B2 cohort were malignant. In contrast to the findings of Wharry *et al.*[10], this suggests that high-quality ultrasonographic assessment may remain negatively predictive, even in large nodules. The discrepancy in the results possibly

relates to the improvement of high-resolution ultrasonographic technology or to the selection bias associated with the analysis of surgically managed cohorts. However, it is a relative strength that, in both the study by Wharry *et al.*[10] and the present study, the surgical pathology of each nodule was confirmed. Further, these data have been generated from real-world surgical practice, informed by the relevant imaging and cytopathological guidelines. Hence these results are of practical relevance to clinical decision-making; in the presence of highly suspicious ultrasonographic characteristics, a benign FNA result must be interpreted with caution and a diagnostic hemithyroidectomy is an appropriate management strategy.

This study has several limitations, including its retrospective design, the potential inter- and intra-observer variability in the interpretation of imaging and cytopathology[11,12], and the selection bias, due to the exclusion of benign thyroid nodules managed non-operatively, which may contribute to the overestimation of risk of malignancy associated with T5 B2 nodules.

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Author contributions

Laura E. Nicholls (Data curation, Formal analysis, Writing—original draft, Writing—review & editing), Alexander Papachristos (Conceptualization, Formal analysis, Supervision, Writing—review & editing), Cici Guo (Data curation, Formal analysis, Writing—original draft), Adam Aniss (Data curation, Writing—review & editing), Anthony R. Glover (Supervision, Writing—review & editing), Mark S. Sywak (Funding acquisition, Resources, Supervision, Writing—review & editing), and Stan B. Sidhu (Funding acquisition, Resources, Supervision, Writing—review & editing).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The participants of this study did not give written consent for their data to be shared publicly; therefore, due to the sensitive nature of the research, supporting data are not available.

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