

## Do sonographic and cytological features predict malignancy in cytologically indeterminate thyroid nodules?

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### ABSTRACT

**INTRODUCTION** The current algorithm for managing patients with indeterminate (Thy3) thyroid cytology is a thyroid lobectomy followed by a completion thyroidectomy depending on histology. We investigated whether sonographic and or cytological features in addition to clinical characteristics would predict the potential for malignancy in a cohort of patients with thyroid nodules of indeterminate cytology.

**METHODS** Perusing a clinical database of all patients undergoing ultrasonography guided fine needle aspiration (FNA) of thyroid nodules, we identified all Thy3 lesions. The demographic, ultrasonography and cytological details of benign and malignant groups were compared by t-test, chi-square test and, when appropriate, Fisher's exact test. Association between studied characteristics and malignancy was tested by binary logistic regression using single input. A *p*-value of <0.05 was considered significant.

**RESULTS** During the retrospective study period of January 2003 to July 2010, a total of 1,019 patients underwent FNA, of which 69 (6.8%) were classed as Thy3. Of these, 59 underwent surgical treatment and the histological outcomes were grouped as benign (*n*=42, 71.2%) and malignant (*n*=17, 28.8%). These groups were analysed for the predictive variables. Age, sex and sonological characters were similar in the two groups (*p*>0.05). The two microcalcifications observed were both in the malignant group. Among all the variables assessed, only the absence of normal follicular cells was associated with malignant nodules (univariate analysis, *p*=0.034).

**CONCLUSIONS** Malignancy was more common in Thy3 patients with an absence of normal follicular cells and such patients may therefore warrant a total thyroidectomy.

### KEYWORDS

Thyroid nodule – Fine needle aspiration – Ultrasonography – Surgery

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### CORRESPONDENCE TO

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Fine needle aspiration (FNA) with or without ultrasonography guidance is an essential part of the assessment of a solitary thyroid nodule. A normal FNA is dependent on the presence of normal follicular cells, macrophages and the presence of colloids in the specimen. A major problem with FNA has been the differentiation of Hürthle cell or follicular cell neoplasms from their malignant counterparts. Indeterminate (Thy3) cytology represents about 10–30% of all aspirates<sup>1,2</sup> and presents a diagnostic dilemma. There have been efforts to identify some criteria to predict malignancy in these nodules. Some studies suggest that male sex, age and nodule size, borders, shape, hypoechoogenicity and microcalcification are risk factors for malignancy in indeterminate follicular lesions<sup>1,5–7</sup> but other studies show no evidence for this.<sup>8–11</sup> The reported malignancy rate within indetermi-

nate lesions varies between 3% and 51%.<sup>5,5,12,15</sup>

The current guideline for managing patients with a follicular lesion or a suspected follicular neoplasm (Thy3) is an initial thyroid lobectomy followed by a completion thyroidectomy for those with a confirmed carcinoma.<sup>14,15</sup> In patients with indeterminate FNA, methods to identify those at highest risk of malignancy may allow the surgeon to perform a single definitive operation, thereby decreasing perioperative morbidity and expediting adjuvant therapy.

We examined the various cytological features of indeterminate thyroid FNA along with known clinical and sonological risk factors to determine whether any parameters were predictive of malignancy.

Table 1 Pathological diagnosis in 59 study patients

Diagnosis	Number of patients
Benign	42 (71.2%)
Follicular carcinoma	6 (10.2%)
Papillary carcinoma	8 (13.6%)
Hürthle cell carcinoma	2 (3.4%)
Anaplastic carcinoma	1 (1.6%)
<b>Total</b>	<b>59 (100%)</b>

## Methods

A clinical database of patients who underwent ultrasonography guided FNA of thyroid nodules between January 2005 and July 2010 at a tertiary referral centre was studied retrospectively. We collated data on patient demographics, nodule cytology, ultrasonography, treatment and final histology. All the relevant parameters were compared between the benign and malignant groups.

The sonographic features of thyroid nodules with respect to size, echo structure, increased vascularity, presence of calcification (in particular microcalcification) and presence of abnormal lymph nodes were analysed. Cytological features including the absence of normal follicular cells, scant or absent colloid and the absence of macrophages were also studied. Univariate associations between the presence of cancer and discrete variables were evaluated using a chi-square test or Fisher's exact test and associations were further confirmed with binary logistic regression using a single input. An unpaired t-test was used for continuous variables. All statistical analyses were performed using SPSS® v18.0 (SPSS Inc, Chicago, IL, US). A *p*-value of <0.05 was considered significant.

## Results

During the study period (January 2005 to July 2010), a total of 1,019 patients underwent ultrasonography guided FNA of the thyroid nodule. Of these, 69 patients (6.8%) had Thy3 cytology at the initial FNA. Repeat cytology confirmed a benign nodule (Thy2) in 7 patients and a further 5 patients were deemed unfit for surgical treatment, leaving a total of 59 Thy3 patients who had surgical treatment and, consequently, a histological diagnosis for analysis. Patients were divided into benign (*n*=42, 71.2%) and malignant (*n*=17, 28.8%) groups. The details of the pathological outcome in the 59 patients studied are given in Table 1. The mean nodule size for the whole study group was 34.2mm (standard deviation [SD]: 14.9mm). Cancer prevalence in different sized nodules is summarised in Table 2. There was no increase in the prevalence of malignancy in larger nodules.

The patient characteristics, ultrasound and cytological details of both benign and malignant nodules are given in Table 3. With regard to age (*p*=0.073) and sex (*p*=0.628), no differences were found between patients with malignant or benign nodules. Ultrasonography characteristics including

Table 2 Risk of cancer in thyroid nodule based on diameter of lesion

Size of nodule	Number of patients	Number of patients with cancer
≤10mm	4	1 (25%)
11–20mm	12	3 (25%)
21–30mm	12	4 (33%)
31–40mm	12	3 (25%)
>40mm	19	6 (32%)

nodule size, calcifications, echo structure, increased nodule vascular flow and cervical lymphadenopathy were similar in both groups (*p*>0.05). Furthermore, the mean nodule size for carcinomas (34.0mm, SD: 15.3mm) did not differ much to the mean nodule size for benign lesions (34.4mm, SD: 14.9mm). Only two patients were found to have microcalcifications and both were in the malignant group. The absence of macrophages and colloid in cytology specimen was similar in both groups and did not correlate with the outcome in these patients.

Normal follicular cells were absent significantly more in malignant than in benign nodules (58.8% vs 28.6%, *p*<0.05) (Table 3). When examined using binary logistic regression (univariate analysis), only the absence of normal follicular cells showed a significant association with malignancy (hazard ratio: 3.57; 95% confidence interval 1.10–11.57; *p*=0.034).

All Thy3 patients with confirmed malignancy underwent a completion thyroidectomy after the initial thyroid lobectomy and a further two patients with extensive bilobar benign lesions underwent a total thyroidectomy.

## Discussion

Thyroid FNA is sufficiently sensitive to categorise thyroid nodules as benign or malignant in the majority of nodular thyroid lesions.<sup>5,16</sup> However, the category of indeterminate follicular lesions continues to present a clinical dilemma. We found that indeterminate lesions accounted for 6.8% of thyroid cytology in our study population, a figure that is similar to other reported studies.<sup>1,2</sup> Approximately 25% of nodules with indeterminate cytology are eventually found to be malignant at surgery<sup>2,3</sup> and we found a similar malignancy rate (28%) in our indeterminate cytology group. Due to the high prevalence of cancer in indeterminate thyroid nodules, current guidelines recommend a thyroid lobectomy as the initial surgical treatment, followed by a completion thyroidectomy in those cases confirmed to have malignancy.

In order to simplify the treatment algorithm and to reduce the morbidity associated with the current regime, several authors have attempted to further classify a subset of nodules based on several clinical features and cytological characteristics to better predict malignancy in such indeterminate nodules.<sup>1,4,5,7,17,18</sup> The clinical features previously explored and suggested to be indicative of a malignant in-

Table 3 Patient characteristics, ultrasound features and cytological details of thyroid nodules of benign and malignant groups

	Benign (n=42)	Malignant (n=17)	p-value
Median age (range)	49.5 (18–77)	38 (22–68)	0.073*
Male	7	2	0.628
<b>Ultrasound features</b>			
Mean nodule size	34.4mm	34.0mm	0.903*
Solid echo structure	18	10	
Cystic echo structure	4	1	
Mixed echo structure	20	6	0.307
Calcification present	5	3	0.678
Microcalcification present	0	2	0.15
Increased nodule vascularity	8	4	0.729
Cervical lymphadenopathy	1	2	0.197
<b>FNA details</b>			
Macrophage absent	31	15	0.310
Colloid absent	19	11	0.252
Normal follicular cells absent	12	10	0.040

FNA = fine needle aspiration

\*Mann–Whitney U test

dex nodule include male sex, younger age, larger diameter, fixity of the mass to surrounding tissues, hypoechogenicity and microcalcifications within the nodules.<sup>1,5–5,7,12,15</sup> However, other authors have reported the relative lack of accuracy of the clinical parameters in predicting malignancy in indeterminate thyroid nodules.<sup>8–10</sup> A study published in 2008 evaluated the role of surgeon-performed ultrasonography in predicting malignancy in patients with indeterminate thyroid nodules.<sup>6</sup> Sonographic features including the nodule's margin, shape, echo structure, echogenicity and presence of calcification have failed consistently to predict malignancy in follicular neoplasms with indeterminate cytology.<sup>19</sup>

In the current study, although we investigated several clinical parameters, sonological and cytological characteristics, only the absence of normal follicular cells in FNA was predictive of malignant lesions, supporting the findings of previous reports.<sup>9,10,15</sup> Our inability consistently to demonstrate other examined parameters to predict malignancy despite it being reported by previous authors could be partly explained by the relatively small sample size. Cytologically indeterminate thyroid nodules are a relative rarity and our study, which involved more than 1,000 patients, underpins the need for prospective, multi-institutional studies to answer this clinically important question given the high incidence of malignancy in these patients.

The ability of clinical features, sonographic parameters and cytological characteristics consistently to predict malignancy in indeterminate thyroid nodules remains less than optimal. This situation has prompted several investigators to seek molecular markers for malignancy in indeterminate follicular lesions. Recent advances in molecular diagnostics including immunocytochemistry, enzyme activity assays

and quantitative reverse transcription polymerase chain reaction have made it possible to analyse products from FNA further. At least 50 molecular markers have been analysed in patients with thyroid nodules,<sup>2</sup> and immunocytochemistry for thyroid peroxidase<sup>20</sup> and galectin-3<sup>21</sup> seems to be particularly promising in predicting malignancy. Theoretically, using the galectin-3 marker routinely could avoid many unnecessary surgical thyroid procedures but this approach is limited by the high false negativity of galectin-3.<sup>22</sup>

Combining the expression of other markers such as human mesothelial antigen and cytokeratin-19, which are expressed in thyroid cancers, and thyroid peroxidase, which is down-regulated in thyroid cancer tissue, might further improve the diagnostic accuracy of immunocytochemistry in such situations.<sup>23</sup> However, use of any of these methods routinely should be carefully assessed in respect to their cost-effectiveness.

## Conclusions

Our results show that malignancy in cytologically indeterminate (Thy3) thyroid nodules is more common in cases with an absence of normal follicular cells. For all other parameters examined in this study we failed to find a statistical difference. Further research to seek accurate predictors of malignancy in cytologically indeterminate thyroid nodules should continue so that surgical treatment can be simplified to a single operation.

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