

# Prevalence of Cancer in Patients with Thyroid Nodules in the Island of Cyprus: Predictive Value of Ultrasound Features and Thyroid Autoimmune Status

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## Key Words

Thyroid nodules · Cancer · Fine needle aspiration · Ultrasound

## Abstract

**Background:** The purpose of this study was to determine the prevalence of thyroid carcinoma in patients who underwent ultrasound-guided fine needle aspiration biopsy (USgFNA) of thyroid nodules in the island of Cyprus. Ultrasound features as well as the presence of autoimmune thyroid disease were evaluated as risk factors for malignancy. **Methods:** 322 consecutively examined patients (272 females/50 males, age 13–81) underwent USgFNA of thyroid nodules in a referral endocrine clinic between July 2007 and July 2009. The ultrasonographic characteristics examined were: echogenicity, margin irregularity, composition, calcifications, presence of increased vasculature and nodule size. The presence or absence of autoimmune thyroid disease was recorded. **Results:** From the 548 nodules examined, 74 (13.6%) were classified as THY3, 4 or 5. 75 patients (123 nodules) underwent surgical resection. 46 patients (64 nodules) proved to have thyroid carcinoma by histology. There was a significant correlation of suspicious/malignant cytology with solid composition, hypoechogenicity, irregular margins and the presence of calcifications. A significant association was also noted be-

tween the presence of positive antithyroglobulin antibodies ( $p < 0.05$ ) and Graves' disease ( $p = 0.01$ ) with suspicious/malignant cytology. **Conclusion:** The overall prevalence of thyroid cancer was 14.3%. Ultrasound characteristics were highly predictive of thyroid malignancy. Thyroid autoimmunity should be considered as a risk factor.

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## Introduction

Thyroid nodules are extremely common with a prevalence of about 20–76% of the adult population based on detection by ultrasonography [1]. Thyroid cancer is rare; however, in the past few decades its incidence has significantly increased [2]. Thyroid cancer is present in approximately 5% of nodules, even though rates as high as 15% have been reported [1, 3, 4]. Fine needle aspiration biopsy is the clinical procedure of choice for evaluating whether a nodule is benign or malignant [3, 5–7]. It is a simple, safe and most accurate method for selecting the patients who will need surgical resection or follow-up. Ultrasound-guided FNA (USgFNA) has improved diagnostic accuracy compared to FNA by palpation [8, 9].

Both the European Thyroid Association and the American Thyroid Association have issued clinical practice guidelines and recommendations as to how to evaluate thyroid nodules [10, 11]. Nodules that are usually 1.0 cm or greater in dimension and are nonfunctioning require further evaluation by FNA. If the TSH is suppressed, then radionuclide scintigraphy is indicated to rule out a functioning nodule. Nodules that are less than 1.0 cm but have suspicious ultrasound characteristics also require further investigation. These characteristics are: hypoechoogenicity, microcalcifications, irregular margins, intranodular vascularity and regional lymphadenopathy [10, 11].

Thyroid cancer in Europe affects approximately 24,826 individuals annually, with an estimated mortality rate of 5,993 patients each year [12]. Studies have shown a true rise in the incidence of micro and larger forms of papillary thyroid carcinoma in northwestern Spain, a higher incidence of thyroid cancer in the volcanic area of Sicily as well as an increasing prevalence of papillary thyroid carcinoma in Greece [13–16]. A recent epidemiological study by Farazi [17] showed that in Cypriot women in 2008 thyroid cancer was the second most common cancer after breast cancer, and that the rates for thyroid cancer in women have doubled in just 1 decade.

Since current data on the incidence of thyroid cancer in nodules in Cyprus do not exist, the purpose of this study was to assess the prevalence of thyroid carcinoma in USgFNA-biopsied nodules of patients in Cyprus. This investigation was a retrospective review of the records of all patients who had USgFNA in a referral endocrine clinic within a 2-year period. Parallel to malignancy assessment, sonographic features as well as the presence of autoimmune thyroid disease were evaluated as potential risk factors.

## Patients and Methods

322 consecutively examined patients (272 female and 50 male), aged 13–81, were included in this study. These patients underwent USgFNA of thyroid nodules at the Nicosia Endocrinology Center, Nicosia, Cyprus, during the period from July 2007 to July 2009. The Nicosia Endocrinology Center is a physician-owned private clinic with referrals for thyroid nodule assessment throughout Cyprus. After history taking, physical examination and a detailed thyroid and neck ultrasonographic examination, TSH levels were measured. If the TSH was not suppressed, USgFNA was performed on all nodules larger than 10 mm or on nodules smaller than 10 mm if there were any suspicious characteristics on ultrasonography. If the TSH was suppressed, then a radionuclide scan was obtained, and autonomously functioning nodules were not aspirated. The diagnosis of autoimmune thyroid disease (Hashimoto's thy-

roiditis and Graves' disease) was based on a combination of detailed history taking, clinical and ultrasonographic examination and the presence of positive thyroid autoantibodies.

FNA was performed under ultrasound guidance. Informed consent was obtained from all patients after explanation of the procedure [18]. A range of 1–4 aspirates was performed per nodule using a 23- to 25-gauge needle attached to a 10-ml syringe. However, the majority of patients had at least 2–3 aspirates per nodule. The aspirated material was then directly smeared onto glass slides for alcohol-fixed and air-dried preparation. The slides were subsequently interpreted by an experienced cytopathologist at the Hammersmith Hospital, London, UK. In addition to conventional slides, in about 40% of the nodules part of the aspirated material was collected in liquid-based cytology vials (CytoLyt, Cytyc Corp., Marlborough, Mass., USA).

Diagnostic cytology was classified according to the British Thyroid Association guidelines as follows: THY1 = nondiagnostic; THY2 = benign (nonneoplastic); THY3 = indeterminate including follicular lesions; THY4 = suspicious for malignancy; THY5 = diagnostic of malignancy [19].

Patients with nodules with FNA cytology suspicious or diagnostic of malignancy (THY4, THY5) or suggestive of follicular neoplasm (THY3) were referred for surgical resection. In addition, some patients with THY2 cytology were also referred for surgery if there were any suspicious ultrasound characteristics. Following surgery, the final diagnosis was based on histopathological examination of the nodule and the entire gland. In the case a particular nodule underwent more than 1 biopsy during the review period, only the most recent FNA was included in the data analysis.

Thyroid ultrasonography was always performed before and during the FNA procedure by a single endocrinologist with special expertise in thyroid neck sonography using a 13-MHz linear transducer. The number and characteristics of nodules were recorded. For each nodule the following were determined: (a) size, as three orthogonal dimensions, (b) echogenicity, (c) irregularity of margins, (d) presence or absence of calcifications, (e) presence of prominent peripheral and/or intranodular vascularity and (f) parenchymal composition (solid, cystic or complex). The location of the nodules was always noted in a detailed thyroid ultrasound diagram (both before and during FNA), and the cytology results were always matched and correlated with the histopathological examination in the patients who underwent surgery. Nodules were characterized solitary only if there was only 1 nodule in the gland, or multiple (multinodular). In multinodular glands, USgFNA was performed on all nodules above 1.0 cm or if a nodule was smaller but had suspicious ultrasound characteristics.

The study protocol was formally submitted for approval to the Cyprus National Bioethics Committee, which advised us that as this was a retrospective record analysis, ethical clearance was not warranted. Patient identities and personal data were not revealed and were kept fully confidential throughout the study analysis.

Results were analyzed on a per-patient and per-nodule basis. Statistical comparisons were based on the analysis of contingency tables (tables 1, 2) which were analyzed using the  $\chi^2$  test (or Fisher test) in order to determine the statistical association between the cross-classified medical characteristics. The significance level of the statistical tests was set to 5%, that is, if the statistical test was found significant, we accepted that the two cross-classified variables are not independent and the observed frequencies depend on the levels (or categories) of factors shown in tables 1 and 2.

**Table 1.** Ultrasound characteristics of thyroid nodules and cytology (n = 548)

	THY1	THY2	THY3	THY4	THY5	p value
Echogenicity						<0.001
Isoechoic/hyperechoic	4	106	3	0	2	
Hypoechoic	6	146	17	12	23	
Margin irregularity						<0.001
Poorly defined	2	28	11	5	16	
Well-defined	14	422	13	14	13	
Composition						<0.01
Solid	1	61	2	0	7	
Cystic	2	13	1	1	0	
Complex	1	140	4	5	0	
Calcifications						<0.001
None	14	406	15	11	13	
Micro	1	30	8	7	14	
Macro	16	10	0	0	1	
Rim	6	5	0	2	0	
Peripheral	7	3	1	0	4	
Vascularity						n.s.
Presence of increased vascularity	2	90	3	2	3	
Absence of increased vascularity	14	330	21	18	25	
Size						n.s.
≤9.9 mm	11	148	14	10	9	
>9.9 mm	5	310	11	10	20	

p value: association between ultrasound characteristics and THY4 + THY5 cytology ( $\chi^2$  test or Fisher test was used); n.s. = not significant.

**Table 2.** Cytology and association with autoimmune thyroid disease (n = 528)

Cytology	Nodules in patients without autoimmune thyroid disease	Nodules in patients with Hashimoto's thyroiditis	Nodules in patients with Graves' disease
THY1 + THY2	293	137	25
THY3	16	6	3
THY4 + THY5	23	18	7

Graves' disease and THY4 + THY5 cytology: p = 0.01. Hashimoto's thyroiditis and THY4 + THY5 cytology: not significant.

## Results

### Patient Characteristics

322 individuals, 272 females (84.5%) and 50 males (15.5%), with ages ranging from 13 to 81 years, mean  $45.0 \pm 13.7$  SD, were included in the study. 203 patients did not have an underlying autoimmune thyroiditis, 97 patients had Hashimoto's thyroiditis, and 22 patients had Graves' disease. A total of 548 nodules were examined with USgFNA. 356 (65.0%) of those nodules were above

9.9 mm and 192 (35.0%) were below or equal to 9.9 mm. Of the 322 patients, 96 (29.8%) had solitary nodules, and 226 (70.2%) had multiple nodules.

### Cytology Results

Out of 548 nodules, 16 were classified as nondiagnostic (THY1; 2.9%), 458 as benign (THY2; 83.6%), 25 as indeterminate/follicular lesions (THY3; 4.6%), 20 as suspicious for malignancy (THY4; 3.7%) and 29 as diagnostic of malignancy (THY5; 5.3%).

### *Histopathology Results*

A total of 75 patients (123 nodules) underwent surgical resection. In this group, 46 patients had carcinoma (61.3%; 44 papillary, 1 follicular, 1 medullary) and 29 had a benign histology (38.7%). Of the 48 nodules that were THY4 + THY5, 46 were histologically confirmed malignant (positive predictive value 95.8%). 10 nodules out of the 17 with THY3 (58.8%) were also malignant. Of the 63 nodules confirmed malignant with histopathology, 23 were  $\leq 9.9$  mm and 40 were  $>9.9$  mm. There was a significant concordance between cytology and histopathology results ( $\chi^2$  test,  $p < 0.01$ ). Overall, the thyroid cancer prevalence was 14.3% (46/322).

In 6 patients, 7 nodules had a benign cytology (THY2) and histologically were proved to harbor malignancy. In 4 of these patients those nodules were present in multinodular glands with other cytologically suspicious nodules (and were thus referred for surgery). The remaining 2 patients were referred for surgery based on the ultrasound characteristics of the nodules. One of those had an elevated serum calcitonin level.

### *Ultrasound Characteristics of Nodules and Correlation with Cytology*

As table 1 shows, the nodule characteristics that showed a significant correlation with THY4 + THY5 cytology ( $p < 0.01$ ) were: hypoechogenicity, margin irregularity, solid composition and the presence of calcifications. No significant association was shown between the presence of increased vascularity and the size of nodules (above or below 9.9 mm).

### *Cytology and Association with Autoimmune Thyroid Disease*

A significant association was noted ( $p < 0.05$ ) between the presence of antithyroglobulin (anti-Tg) antibodies (Abs) and THY4 + THY5 cytology. No significant association was shown between the presence of anti-thyroid peroxidase Abs and THY4 + THY5 cytology. A significantly higher percentage of THY4 + THY5 cytology was found in anti-Tg Ab+ nodules (15.2%) compared to anti-Tg Ab- nodules (8.2%). Overall, 16.1% (18/112) of anti-Tg Ab+ nodules were histologically proven to be malignant whereas the prevalence of malignancy in anti-Tg Ab- nodules was 12.2% (31/225).

A significant association ( $p = 0.01$ ) was also noted between the presence of Graves' disease and THY4 + THY5 cytology (table 2). 20% of nodules from Graves' disease patients had THY4 + THY5 cytology compared to 6.9%

of nodules from patients without Graves' disease. No association was found between Hashimoto's thyroiditis and THY4 + THY5 cytology.

### **Discussion**

The goal of this study was to determine the rate of malignancy in patients with thyroid nodules who underwent USgFNA in a referral endocrine clinic in Cyprus and to examine how ultrasound data and clinical/laboratory information are relevant to cancer risk. We strictly followed the recommendations set by the European Thyroid Association and the American Association of Clinical Endocrinologists, where all nodules above 1 cm should be examined, as well as nodules less than 1 cm but with suspicious ultrasound findings. As such, our data represent thyroid cancer risk/prevalence according to thyroid nodule assessment guidelines. However, as our study group is highly specific, our results are not representative of the entire population of the island.

The overall prevalence of thyroid carcinoma in our study was 14.3%. In the literature, the reported risk of malignancy ranges between 5 and 15% [1, 3, 4, 20]. However, in contrast to our cohort, in previous studies using the same methodology, either only nodules above 10 mm were subjected to FNA (cancer prevalence 14.9%) [4] or only nodules between 8 and 15 mm (cancer prevalence 7.7%) [21], or FNA was done on all nodules above 3 mm (cancer prevalence 21.6%) [9]. Another study from Spain showed a malignancy rate of 24.9% of nodules [22].

We observed a high prevalence of cancer in THY3 nodules, as 58.8% of those proved to be malignant with histology. This data agrees with previously published work about the importance of considering THY3 cytology as a suspicious finding that requires further examination [23, 24] either by surgical excision or with the use of the new commercially available molecular diagnostic tests [25]. A more conservative approach has been suggested for cytologically indeterminate thyroid nodules which are benign according to the gene expression classifier [26] whereas a positive *BRAF* V600E mutation warrants surgery [27, 28].

The results of this study agree with other published studies where solid composition, hypoechogenicity, irregular margins and the presence of calcifications correlate with malignant cytology [4, 9, 21, 29]. We did not find any statistical association between increased nodule vascularity and cancer risk. The rate of inadequate sampling was very low compared to other published studies. This was mostly seen in cystic lesions where the specimen was

low in cellularity. Furthermore, our high positive predictive value of 95.8% indicates that our technique was highly sensitive and accurate, comparable to similar studies from Korea [30], Denmark [31] and Belgium [32]. In our study, most cancers were papillary, and this is in accordance with other studies that showed an increased prevalence of this type of thyroid cancer [9, 33, 34].

An important finding is the association between the presence of positive antithyroid Abs and suspicious/malignant cytology. There are studies published that examined the association between thyroid autoimmunity and cancer [35–38], but it still remains a debatable issue. Anil et al. [39] found no association, although Kim et al. [40] showed that a positive serum Tg Ab is an independent predictor for thyroid malignancy in nodules. Our results agree with a similar study by Boi et al. [41], where in a large series of unselected thyroid nodules subjected to FNA, a higher prevalence of suspicious cytology was shown in patients with positive serum thyroid autoantibodies. A more recent prospective study has shown that in patients with thyroid nodules elevated serum concentration of Tg Ab, but not serum thyroid peroxidase Ab, is

an independent predictor for thyroid cancer [42]. Our findings are also in agreement with studies that showed that patients with Graves' disease are at a higher risk of thyroid carcinoma [43–45].

## Conclusion

The overall prevalence of thyroid carcinoma in our study population with thyroid nodules in Cyprus was 14.3%. Ultrasound characteristics are extremely important in evaluating thyroid nodules. Furthermore since the presence of autoimmune thyroid disease seems to confer an increased risk of malignancy, we suggest that patients undergoing FNA should undergo a complete endocrine evaluation, as this may affect the clinician's decision for FNA especially in small nodules.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

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