Clinical Thyroidology / Original Paper

European
Thyroid Journal

Eur Thyroid J 2018;7:39–43
DOI: 10.1159/000484600

Received: March 30, 2017
Accepted: October 17, 2017
Published online: November 21, 2017

# Indeterminate Thyroid Nodules: A Pragmatic Approach

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**Keywords**
Thyroid nodule · Fine needle aspiration of the thyroid · Ultrasound of the thyroid · Ultrasound risk stratification

**Abstract**
***Background:*** Fine needle aspiration (FNA) cytology fails to provide a conclusive diagnosis in a subset of thyroid lesions labeled as "indeterminate" (Thy3). In this study, we aimed at ascertaining the prevalence of Thy3 thyroid nodules in a hitherto unreported ethnic group (residents of the United Arab Emirates). ***Methods:*** We retrospectively examined 688 FNA of the thyroid performed on 584 patients. Samples were reported using the Royal College of Physicians' (RCP) Thy classification. The results of the FNA were correlated with the final surgical specimens. Ultrasonography (US) risk stratification was calculated using a web-based US risk of malignancy calculator. ***Results:*** Overall sample adequacy was 97%. The indeterminate group Thy3 was found in 7% of the samples. The overall risk of malignancy in the Thy3 category was 20%. This risk was very similar in the 2 subgroups of Thy3 (17% in Thy 3a and 22% in Thy3f). Subdividing the Thy3 group into subgroups becomes less necessary if the US scoring is <24.5% since the negative predictive value, in this case, is 100%. Applying this criterion to our population would have had the potential of reducing the percentage of patients referred to surgery from 61 to 43%. ***Conclusions:*** Proper risk stratification of Thy3 lesions should be based on the combined risk assessment of clinical, cytological, radiological, and molecular data. Such a pragmatic approach is expected to reduce the percentage of inappropriate referrals to surgery.



## Introduction

The prevalence of thyroid nodules is population dependent and increases with age and with the use of thyroid ultrasonography (US). It is estimated to be 2–6% with palpation, 19–68% with US, and 8–65% in autopsy specimens [1]. The ultimate goal of the diagnostic evaluation of a thyroid nodule is to determine whether it is benign or malignant and consequently to provide timely and appropriate treatment. Fine needle aspiration cytology (FNAC) of the thyroid nodule is currently the primary diagnostic tool for determining the nature of a thyroid nodule. Its yield increases if done under ultrasound guidance [2–7]. However, it fails to provide a conclusive result in a subset of patients, labeled as having an "indeterminate" diagnosis or Thy3 [8, 9]. The reported risk of

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malignancy in this group is variable among different centers, ranging from 6 to 48% [10]. In this regard, the role of ultrasound has emerged as a practical and accurate tool in the risk stratification of such nodules [2, 3, 11, 12].

Our objectives were to assess the hitherto unreported prevalence of Thy3 lesions of thyroid nodules among residents of the United Arab Emirates and to correlate cytological and pathological diagnoses in this group. We also aimed to assess whether combining FNAC with US risk stratification preoperatively would increase the predictive value for malignancy in this group and allow for better appropriately tailored surgical decision making.

## Subjects and Methods

Cytological diagnoses were undertaken in 688 thyroid nodules from 584 patients evaluated by ultrasound-guided FNA (USG-FNA) at the authors' institution. Ultrasound was performed with 9–12 MHz linear array transducer (eLogic GE). The same endocrinologist performed real-time US and FNA procedures. USG-FNA was performed for the nodules presenting suspicious US features; when no such features were identified, USG-FNA was performed on the largest of multiple nodules. USG-FNA was performed with a 23-G needle using a capillary method. The resulting material was expelled onto glass slides; part of it was smeared immediately for Quick-Diff rapid on-site assessment (ROSE) by a cytologist, and the remainder was air dried for May-Grünwald Giemsa staining or fixed in 95% ethyl alcohol for Papanicolaou staining. Slides were dispatched to Hammersmith Hospital in London and were analyzed by a single experienced cytopathologist. FNA cytology was interpreted according to the Royal College of Physicians [13].

A 14-point validated web-based US risk of malignancy calculator was used retrospectively. Ultrasound features such as solid content, taller-than-wide shape, spiculated margin, ill-defined margin, hypoechogenicity, marked hypoechogenicity, microcalcifications, and rim calcifications are considered predictors for malignant nodules. Malignancy risk ranges widely between 3.8 and 97.4%, and the risk of malignancy is positively associated with increases in risk scores [14, 15].

Institutional approval was obtained to collect the data for this study. The results of the FNA were correlated with the final surgical specimens. The cytopathologist was blinded to the results of the final pathology. Finally, a small analysis of our cytology results was correlated with those obtained from a similar study with a different ethnic background (London, UK) and performed by the same cytologist.

## Results

The adequacy rate of our cytological samples was 97%. The concordance rate of our cytology with surgical pathology was 100% for the Thy5 subgroup and 83% for the Thy4 subgroup (suspicious for malignancy); 85% of the whole sample were consistent with a benign diagnosis, and 7% (49/688) were categorized as Thy3 (Thy3f: 3.9% and Thy3a: 3.1%) (Tables 1, 2).

Of the total 49 patients with the Thy3 category, 30 (61%) patients underwent surgery, of whom 12 were from the Thy3a subgroup (40%) and 18 from the Thy3f subgroup (60%). The decision not to refer for surgery was

**Table 1.** Thyroid FNA results in Abu Dhabi (2013–2015) and London (2014)

| Cytology ICLDC | Definition | Surgical pathology | |
|---|---|---|---|
| | | Abu Dhabi ($n$ = 688) | London ($n$ = 1,276) |
| Thy1 | Nondiagnostic | 3% | 11% |
| Thy2 | Nonneoplastic/cystic | 85% | 72% |
| Thy3 | | 7% | 8% |
| Thy3a | *Neoplasm possible; atypia/nondiagnostic* | 3.1% | |
| Thy3f | *Neoplasm possible, suggesting follicular neoplasm* | 3.9% | |
| Thy4 | | 1% | 4% |
| Thy5 | | 4% | 5% |

ICLDC, Imperial College London Diabetes Center, Abu Dhabi.

**Table 2.** Correlation of Thy3 (indeterminate group) with surgical pathology

| Cytology | Surgical pathology | |
|---|---|---|
| | benign | malignant |
| Thy3 | 80% | 20% |
| Thy3a | 83% | 17% |
| Thy3f | 78% | 22% |

**Table 3.** US risk scoring for malignancy

| US risk scoring | Negative predictive value | Positive predictive value |
|---|---|---|
| <24% | 100% | |
| >48% | | 50% |
| >65% | | 76% |

US, ultrasonography.

based on either low-risk stratification or the patients refusing to opt for surgery. Four patients in the 2 subgroups were lost to follow-up.

As a whole, 80% of the nodules in the Thy3 subgroup were benign and 20% malignant. More specifically, 83% were benign and 17% malignant in the Thy3a subgroup and 78% were benign and 22% malignant in the Thy3f subgroup. All Thy3 patients found malignant at surgery had a US risk score >35%, and a scoring of <24.5% had a negative predictive value (NPV) of 100% (9/9). If a US risk of malignancy of ≥48% in this group is considered, there is a 50% chance that malignant case lesions are identified. On the other hand, a score of >65% among the 3 groups (Thy3, thy4, and Thy5) correlated with a positive predictive value (PPV) of 76% (Table 3).

A parallel and subsidiary analysis was done to assess the follow-up of our Thy2 lesions. Of an initial group of 445 Thy2 lesions, 236 were lost to follow-up; 86 among the remaining 209 Thy2 lesions that were followed up for an average time of 16 months (range 1–41) had a repeat biopsy. Of these, 75 (86%) remained as Thy2, and 11 (12%) were reclassified as Thy3 (10%), Thy4 (1%), and Thy5 (1%), respectively (Fig. 1).

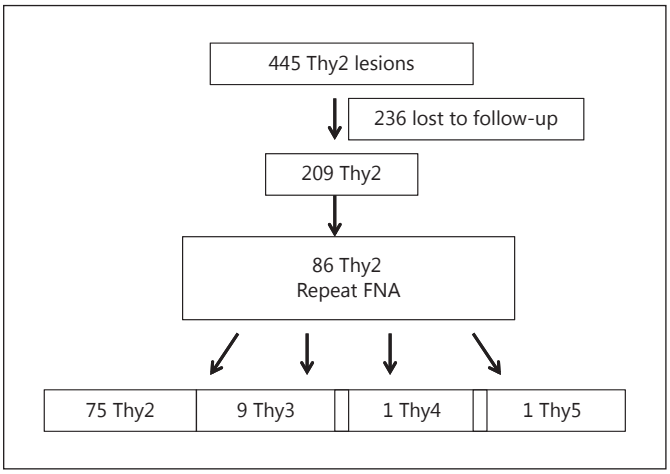


**Fig. 1.** Follow-up of patients with Thy2 lesions. Average follow-up time: 16 months (range 1–41).

## Discussion

The ultimate goal of the diagnostic evaluation of a thyroid nodule is to determine whether it is benign or malignant in order to provide timely and appropriate treatment.

FNA remains the primary diagnostic intervention for the evaluation of most thyroid nodules [2, 3, 11, 12]. FNAC establishes a reliable diagnosis in 70–80% of instances, and approximately 15–25% will be classified as indeterminate (often referred to as follicular neoplasm Thy3f or atypia of undetermined significance Thy3a) [8, 9]. However, the risk of malignancy in the Thy3 group could also vary from 25 to 50% due to inter- and intraobserver variability among pathologists, institutional referral patterns, operative selection, the inclusion of incidental microcarcinomas, and publication bias [10, 13, 16, 17].

The overall risk of malignancy in our Thy3 group was 20%. This risk is very similar to that reported by the recently updated Italian risk classification but [11] dissimilar in that the observed risk difference between our 2 subgroups of Thy3 was minimal (17% in Thy3a and 22% in Thy3f). This observation could be a valid finding specific to our population or random phenomena explained by the small size of our sample. It is also interesting to note that the proportion of biopsies classified as indeterminate was the same between the 2 different ethnic groups (Table 1). Of relevance, 86% of our Thy2 lesions remained negative after an average follow-up time of 16 months (average 1–41), and 14% were reclassified as Thy3, Thy4, and Thy5. If one considers the overall risk of malignancy to be 20% in the Thy3 group, only 4/86 patients (4–5%) would have been falsely labeled as negative. This latter figure is consistent with the 3–5% false negative rate reported by most reputable cytological reporting systems in the Thy2 group [9–11].

Ultrasound of the thyroid has emerged as a useful tool to improve the risk stratification for malignancy in thyroid nodules. Single ultrasound features show inconsistent predictive values, and the combination of ultrasound findings improves their PPV [2, 3, 18, 19]. In this regard, different international societies have published their thyroid ultrasound risk stratification systems to give thyroidologists a practical tool to use [2, 3, 11, 12]. However, a recent study by Trimboli et al. [20] looked at the accuracy of international risk stratification systems in thyroid lesions classified as indeterminate. Poor accuracy (up to 54%) and specificity (up to 19%) were recorded among all reporting systems. The highest sensitivity (91%) and NPV (94%) was obtained by the British Thyroid Association (BTA). When the size thresholds proposed by guidelines was considered, the American Thyroid Association (ATA) system reached the highest sensitivity in detecting cancers (95%).

We looked at refining our decision making in the Thy3 thyroid lesions by combining the information gathered from cytology and ultrasound. The calculated web-based US risk of malignancy at <24.5% in our Thy3 group correlated with 100% benign lesions at final surgery. Subdividing the Thy3 group into subgroups becomes less important if the US scoring is <24.5% since the NPV is 100%. Applying this criterion to our population would have had the potential of reducing the percentage of patients referred to surgery from 61 to 43%. Our results concur with those of Grani et al. [21], who reported on the US scoring of 49 patients with indeterminate thyroid nodules. Using either the ATA (very low suspicion) or the TIRADS (category 3 or less) allowed high exclusion confidence of malignancy (NPV of 100%).

Risk stratification could be even further refined using molecular testing. A recent European study reported that the combination of 2 or more of US suspicious features with molecular mutations RAS and BRAF has a high predictive malignancy figure of 100% [22]. Our reasons not to resort to molecular diagnostics were multiple. There is still no consensus on the use of molecular testing in thyroid lesions, no large validated prospective studies are addressing this issue, and the cost of the tests is still prohibitive [2, 3, 23–25].

There are limitations to our study due to its small size and its retrospective nature, and larger studies are needed in this respect. However, our results concur with those recently published.

We have shown that proper risk stratification should take into account the gathering of clinical, radiological, cytological, and even molecular data relevant to each patient. The final calculated risk should then be balanced with the patient's perceptions and discussed in the setting of a multidisciplinary team. This approach will minimize the number of inappropriate referrals to surgery.

## Disclosure Statement

All authors have no conflicts of interest to declare.

## References


1 Mazzaferri EL: Management of a solitary thyroid nodule. New Engl J Med 1993;328:553–559.
2 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1–133.
3 Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, et al: American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules – 2016 Update. Endocr Pract 2016;22:622–639.
4 Alexander EK: Approach to the patient with a cytologically indeterminate thyroid nodule. J Clin Endocrinol Metab 2008;93:4175–4182.
5 Alexander EK, Heering JP, Benson CB, Frates MC, Doubilet PM, Cibas ES, et al: Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. J Clin Endocrinol Metab 2002;87:4924–4927.
6 Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A: Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid 1998;8:15–21.
7 Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ: Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid 1998;8:283–289.
8 Crippa S, Mazzucchelli L, Cibas ES, Ali SZ: The Bethesda System for reporting thyroid fine-needle aspiration specimens. Am J Clin Pathol 2010;134:343–344.
9 Theoharis CG, Schofield KM, Hammers L, Udelsman R, Chhieng DC: The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution. Thyroid 2009;19:1215–1223.
10 Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW: The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol 2012;56:333–339.
11 Fadda G, Diana E: The 2014 Italian Reporting System for Thyroid Cytology: comparison with the national reporting systems and future directions. J Basic Clin Med 2015;4:46–51.
12 Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard GH, et al: Guidelines for the management of thyroid cancer. Clin Endocrinol 2014;8(suppl 1):15–18.
13 Lobo C, McQueen A, Beale T, Kocjan G: The UK Royal College of Pathologists thyroid fine-needle aspiration diagnostic classification is a robust tool for the clinical management of abnormal thyroid nodules. Acta Cytol 2011;55:499–506.
14 Choi YJ, Baek JH, Baek SH, Shim WH, Lee KD, Lee HS, et al: Web-based malignancy risk estimation for thyroid nodules using ultrasonography characteristics: development and validation of a predictive model. Thyroid 2015;25:1306–1312.
15 Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, et al: Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology consensus statement and recommendations. Korean J Radiol 2016;17:370–395.
16 Iskandar ME, Bonomo G, Avadhani V, Persky M, Lucido D, Wang B, et al: Evidence for overestimation of the prevalence of malignancy in indeterminate thyroid nodules classified as Bethesda category III. Surgery 2015;157:510–517.
17 Gerhard R, da Cunha Santos G: Inter- and intraobserver reproducibility of thyroid fine needle aspiration cytology: an analysis of discrepant cases. Cytopathology 2007;18:105–111.
18 Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, et al: Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Intern Med 2013;173:1788–1796.

19 Brito JP, Gionfriddo MR, Al Nofal A, Boehmer KR, Leppin AL, Reading C, et al: The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab 2014;99:1253–1263.
20 Trimboli T, Fulciniti F, Zilioli V, Ceriani L, Giovanella L: Accuracy of international ultrasound risk stratification systems in thyroid lesions cytologically classified as indeterminate. Diagn Cytopathol 2016;45:113–117.
21 Grani G, Lamartina L, Ascoli V, Bosco D, Nardi F, D'Ambrosio F, et al: Ultrasonography scoring systems can rule out malignancy in cytologically indeterminate thyroid nodules. Endocrine 2017;57:256–261.
22 De Napoli L, Bakkar S, Ambrosini CE, Materazzi G, Proietti A, Macerola E, et al: Indeterminate single thyroid nodule: synergistic impact of mutational markers and sonographic features in triaging patients to appropriate surgery. Thyroid 2016;26:390–394.
23 Marti JL, Avadhani V, Donatelli LA, Niyogi S, Wang B, Wong RJ, et al: Wide inter-institutional variation in performance of a molecular classifier for indeterminate thyroid nodules. Ann Surg Oncol 2015;22:3996–4001.
24 Nikoforov YE: Molecular diagnostics of thyroid tumors. Arch Pathol Lab Med 2011;135:569–577.
25 McIver B, Castro MR, Morris JC, Bernet V, Smallridge R, Henry M, et al: An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab 2014;99:4069–4077.