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Adherence to Active Surveillance and Clinical Outcomes in Patients with Indeterminate Thyroid Nodules Not Referred for Thyroidectomy

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Thyroid cancer · Thyroid nodule · Indeterminate cytology · Thyroidectomy · Lobectomy

Abstract
Objective: Outcomes of patients with cytologically indeterminate thyroid nodules not referred for thyroidectomy have hardly been investigated. We previously reported outcomes of 322 patients with thyroid nodules classified according to the Bethesda System of Reporting Thyroid Cytology (BSRTC) as indeterminate (B3/B4), of whom 123 (38.2%) underwent thyroidectomy. In the present extension study, we investigated adherence and outcomes in the remaining unoperated 199 patients. ***Methods:*** We conducted a file review of 189/199 patients with thyroid nodules cytologically diagnosed as B3 (n = 174) or B4 (n = 15) in 2011–2012 who were conservatively followed at our institution until 2019. ***Results:*** Among 174 patients with B3 nodules, 140 (80.4%) underwent repeated ultrasound. Nodular growth was detected in 23 (16.4%), and findings remained stable in 105 (75%). Fine-needle aspiration was repeated in 88/174 patients (50.6%), with B2 results in 62 (70.4%) and B3/B4/B5 in 20 (22.7%). Thyroidectomy was performed in 14/174 patients (8%) in the B3 and 5/15 patients (33%) in the B4 group at a median of 5 years' follow-up; thyroid cancer was diagnosed in 4/14 patients (28.5%) and 3/5 patients (60%), respectively. For B3 patients who remained unoperated, none had evidence of thyroid cancer at last follow-up. A reason for avoiding surgery was documented in 6/10 unoperated B4 patients (1 thyroid lymphoma, 3 died of unrelated causes, 2 were considered inoperable due to advanced age). ***Conclusions:*** Most patients with initially unoperated B3/B4 nodules adhere, at least partially, to active surveillance. For B3 nodules, subsequent thyroidectomy and thyroid cancer detection are rare events, and patients may be safely managed without using molecular markers. Thyroid cancer is diagnosed in most B4 patients who undergo thyroidectomy in our institution.

Introduction

The introduction of the Bethesda System of Reporting Thyroid Cytology (BSRTC) in 2009 provided clinicians with a standardized, category-based system for reporting the results of fine-needle aspiration (FNA) of thyroid specimens. Nodules are divided into 6 diagnostic categories with different implied risk of malignancy (ROM) and clinical management guidelines [1]. According to the original classification, Bethesda III (B3) nodules have a relatively low (5–15%) ROM and might be managed with

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active surveillance or thyroidectomy, depending on clinical considerations. Bethesda IV (B4) nodules are associated with a 15–30% ROM and require surgery [1]. Importantly, the actual incidence of thyroid cancer in operated patients may differ considerably among institutions for several reasons: large inter- and intra-observer variability in the cytology interpretation; the individual experience of the cytologist in the field; and differences in the criteria for referring patients for FNA and surgery [2–4].

In recent years, various molecular diagnostic tests have been implemented, aiming to improve the preoperative evaluation of ROM in cytologically indeterminate thyroid nodules and to prevent unnecessary thyroidectomies [5, 6]. However, incomplete accuracy, limited availability, and high cost restrict their routine use in real-world clinical practice. Additionally, the natural history of mutation-negative yet cytologically indeterminate nodules remains unclear. Moreover, the BSRTC-based estimation of preoperative malignancy risk was challenged by the recent reclassification of some thyroid nodules as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The 2017 revision of the BSRTC includes the updated malignancy risks, the implications of the NIFTP category on the malignancy risk, and the option of molecular testing in B3/B4 nodules [7]. The long-term outcomes of patients with cytologically indeterminate thyroid nodules who are not initially referred for thyroidectomy have hardly been investigated.

In a previous study, we investigated the impact of implementing the BSRTC to detect the rate of thyroidectomy and malignancy in a large cohort of patients with B3/B4 thyroid nodules who did not undergo molecular testing [8]. The present study is an extension analysis of the long-term outcomes of patients from the original cohort who were triaged to active surveillance according to the clinician's risk assessment or the patient's preference.

Methods

This is an extension analysis of our previous study [8] of 3,927 patients who underwent thyroid FNA at our institution from January 2011 to December 2012, of whom 322 (8.2%) were diagnosed with cytologically indeterminate nodules (250 B3, 72 B4) and whose follow-up data were available. Thyroidectomy was performed immediately after diagnosis in 123/322 patients (38.2%): 66/250 (26.4%) were diagnosed with B3 nodules and 57/72 (79.2%) with B4 nodules. Patients were referred for surgery based on clinical and ultrasound (US) criteria, as well as the results of repeated FNA. In none of the patients was molecular analysis of the thyroid nodules performed [8]. On pathological examination, thyroid cancer was diagnosed in 66 (53.7%): 30 (45.4%) were categorized as B3 and 36 (63.1%) as B4. The remaining 199 unoperated patients (61.8%) were triaged to active surveillance.

In the present study, the medical records of the 199 patients with unoperated B3/B4 nodules were reviewed, and the relevant data were collected from the index FNA in 2011–2012 to the most recent visit until June 2019. These data included visits at endocrine clinics as well as the timing and results of neck US and/or additional FNAs. Nodules with a change of ≥20% in the largest diameter were categorized as having grown in size. For patients who underwent thyroidectomy during follow-up, the indication for surgery was documented, and the full pathology report was retrieved.

Statistical Analysis

Numerical data are expressed as mean and SD, and categorical data are expressed as number and percent. Groups of B3/B4 nodules were compared using independent Student *t* test for numerical variables and χ^2 test or Fisher exact test for categorical variables. A p value of <0.05 was considered statistically significant. SPSS software was used for all statistical analyses (IBM SPSS Statistics for Windows, version 24, IBM Corp., Armonk, NY, USA, 2016).

Results

Patient Characteristics

Of the 199 unoperated patients (95%) from our previous study, 10 were lost to follow-up. Of the remaining 189 for whom data were available for analysis, 174 had B3 and 15 had B4 nodules. The mean duration of follow-up was 4.2 ± 2.3 years, with a median of 5 years. The patients' demographic and relevant clinical characteristics are summarized in Table 1. As expected, most patients were female; there were no significant differences in age, risk factors, and nodule size by nodule classification. While only 2 patients with B4 nodules had previous FNA before the index test in 2011–2012, in 52/174 B3 patients (29.9%), previous benign nodule cytology (B2) was recorded in the medical file. None of the patients underwent molecular diagnostic analysis of the nodule during follow-up.

Follow-Up and Thyroidectomy: B3 Group

During follow-up, of the 174 patients with a B3 nodule, 137 (78.7%) visited the endocrine clinic and 140 (80.4%) underwent repeated US. Nodule size remained stable in 105/140 patients (75%), and some growth was detected in 23 patients (16.4%); in 12 patients, data on the change in tumor size were unavailable. FNA was repeated in 88/174 patients (50.6%), leading to the restaging of the nodule to B2 in 62 (70.4%), to B4 in 3 (3.5%), and to B5 in 1. B3 cytology was reconfirmed in 16 patients (18.6%). The remaining 6 patients (7%) had insufficient or unknown FNA results.

Table 1. Characteristics of patients with B3 and B4 thyroid nodules not initially referred for thyroidectomy

Characteristics	B3 (n = 174)	B4 (n = 15)	p value
Female sex	149 (85.6)	14 (93.3)	ns
Age, years	59.7±12.4	60.5±13.8	ns
Risk factors for DTC	12 (6.9)	1 (6.6)	ns
Lesion size, mm	22±10.9	20±9.7	ns
FNA before 2011	68 (39.1)	2 (13.3)	
B2 by FNA before 2011	52 (29.9)	1 (6.7)	

Values are n (%) or mean ± SD. DTC, differentiated thyroid cancer; FNA, fine-needle aspiration; ns, not significant.

Table 2. Indication, surgery type, and pathological findings in patients with B3 thyroid nodules operated during surveillance

Parameters	n (%)
Indication for surgery	
Tumor growth	4 (28.6)
Repeated B4/B5 FNA	4 (28.6)
Toxic multinodular goiter	1 (7.1)
Parathyroid adenoma	1 (7.1)
Large retrosternal MNG	1 (7.1)
Unknown	3 (21.4)
Type of surgery	
Hemithyroidectomy	10 (71.4)
Total thyroidectomy	3 (21.4)
Two stages total	1 (7.1)
Pathology	
Benign	8 (57.1)
Malignant	4 (28.6)
NIFTP	1 (7.1)
Unknown	1 (7.1)

FNA, fine-needle aspiration; MNG, multinodular goiter; NIFTP, noninvasive follicular tumor with papillary-like features.

The last follow-up action (visit in an endocrine clinic/neck US/thyroid FNA) in most patients (105/174, 60.3%) was recorded in 2016–2019, ≥4 years after the index FNA. Of these, 64 patients (36.8%) had documented follow-up in 2018–2019, ≥6 years after the index FNA. However, 23 patients (13.2%) were lost to follow-up within ≤1 year after the index FNA with B3 cytology.

During follow-up, thyroidectomy was performed in 14 of the 174 initially unoperated patients with a B3 nodule (8.0%; Table 2). Indications for surgery were nodule growth in 4 (28.6%), B4/B5 classification on repeated FNA in 4 (28.6%), and others in the rest. The final diagnosis in the patients restaged B4/B5 by FNA was thyroid cancer, Hurtle cell adenoma, and benign nodular goiter in 1 patient each; the final pathology was missing in the fourth patient. Overall, thyroid cancer was diagnosed in 4 of the 14 patients (28.6%) operated during follow-up, for a rate of 2.3% (4/174) for the whole B3 group. Repeated FNA in the 4 patients with cancer yielded B3 in 2 and B5 in 1. The fourth patient underwent thyroidectomy without additional FNA because of a large multinodular goiter; a single 3-mm focus of papillary thyroid carcinoma/follicular variant was found incidentally on histopathology examination. For those who remained unoperated, no clinical evidence of thyroid cancer was present at the end of the study. Twelve patients in the B3 group (6.9%) died between 2011 and 2019, all from unrelated causes.

Follow-Up and Thyroidectomy: B4 Group

In the B4 group, 14/15 patients remained in follow-up after the index FNA performed in 2011–2012. Repeated US was performed in 12/14 patients (85.7%), and tumor growth was seen in 2 of them (14.2%). Nodule size was stable in the others. FNA was repeated in all 14 patients, leading to restaging to B2 in 4 patients and B3 in 1. In another 3 patients, FNA was insufficient for diagnosis. In 6/14 patients (42.9%), the diagnosis remained B4 on repeated FNA.

During follow-up, thyroidectomy was performed in 5/14 patients (35.7%), and the histopathology was consistent with thyroid cancer in 3 of them (60.0%). A benign nodule was found in 2/5 operated patients (40.0%). Of the other 10 unoperated B4 patients, 1 had thyroid lymphoma, 3 died of unrelated causes at 2 years from the original study, and in 2, surgery was ruled out because of advanced age. Of the remaining 4 patients, 3 had no evidence of disease at the last visit, and 1 was lost to follow-up.

An overview of our results in the 322 B3/B4 patients of whom 123 (38.2%) underwent thyroidectomy in our original study [8] and 189 (58.7%) are included in the current extension study is depicted in Figure 1.

Discussion

The present study found that patients with B3 thyroid nodules who were triaged to active surveillance without molecular analysis had a low (<3%) risk of thyroid cancer at a median of 5 years' follow-up. At the same time, in the much smaller group of patients with B4 nodules, a good reason for the decision not to operate was usually evident.

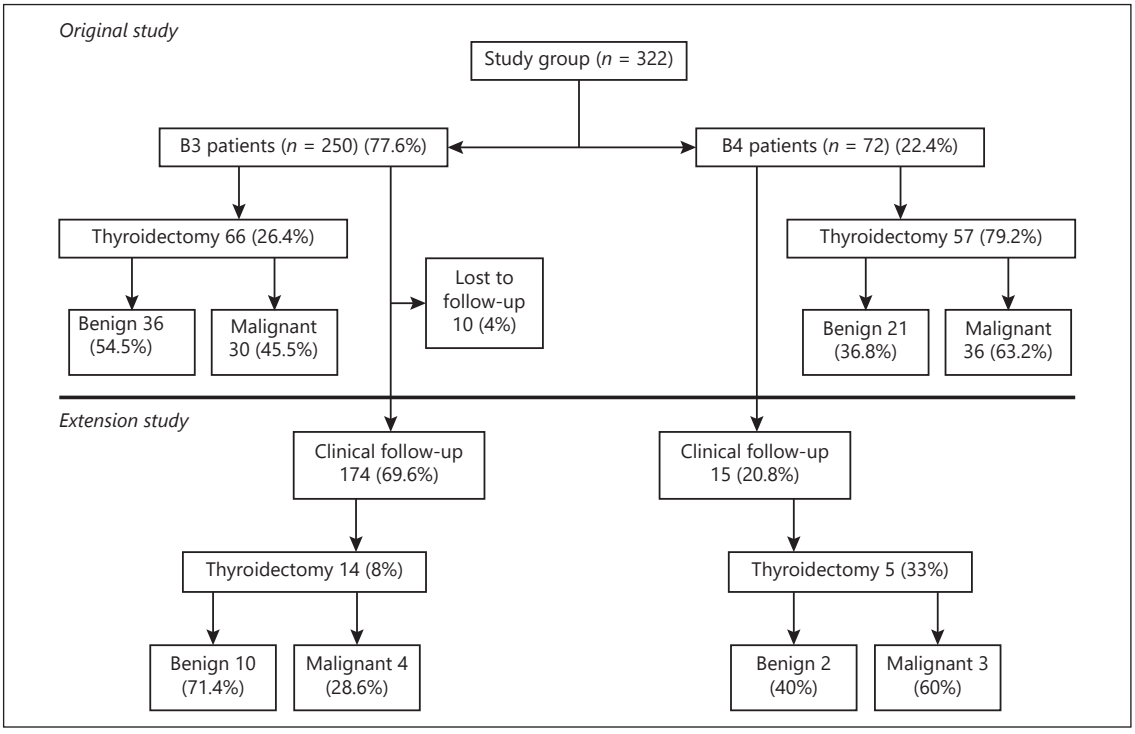

Fig. 1. An overview of our findings in 322 indeterminate thyroid nodules; 123 were operated in the initial study [8], and 189 are included in the current extension study.

In our institution, the preoperative ROM was previously reported to be 45.5% for patients with B3 nodules and 63.2% for patients with B4 nodules [8]. In the present study, we found that most of the unoperated patients in the B3 group remained on active surveillance: approximately 80% attended endocrine clinics and underwent repeated neck US, and 50% had a repeated FNA. Approximately 60% of our B3 patients attended follow-up for ≥4 years after initial diagnosis. Among the 15 initially unoperated B4 patients, only 1 was lost to follow-up. In a study from another large medical center in Israel, only 53% of 48 patients with B3 nodules showed good adherence to active surveillance [9]. Patients were considered lost to follow-up if the last data collection occurred >6 months before the end of the study period [9]. The criteria used to determine optimal adherence in the earlier study may explain the difference from our study.

Molecular testing of thyroid nodules was not performed in any of our patients. The only molecular marker that was available in Israel during most of the study years was gene expression classifier (GEC) analysis (Afirma) based on the mRNA expression pattern in FNA material. Molecular analysis of thyroid nodules is not covered by Israeli public health insurance and costs around 3,200 USD. Given Afirma's high negative predictive value (NPV), with an originally reported false-negative rate of only 5%, it is being used as a rule-out test to avoid unnecessary surgery [10]. However, its NPV was shown to be dependent on the preoperative ROM of each institution [11–13]. While a benign GEC result is reassuring, at least temporarily, it does not obviate the need for follow-up assessment and should not be used as a single criterion to preclude surgery. A recent study by Singer et al. [14] found that of 201 patients with benign/cytologically indeterminate nodules by GEC, 96% had visited the clinic at least once, and 60.2% had undergone at least 1 US scan during a 20-month follow-up period. Moreover, despite the short surveillance time, 11.4% of the patients underwent thyroidectomy [14]. Interestingly, the rates of surgery in the study of Singer et al. [14] using GEC analysis did not differ from the rate in our study (10.9%) without GEC analysis and with a more than two-fold longer follow-up period. Similar rates of thyroidectomy for GEC-negative nodules were reported by Sacks et al. [15], Duick et al. [16], and Alexander et al. [17] (24, 7.6, and 15.5%, respectively).

The pooled data of our initial [8] and current extension studies show that the rate of malignancy in our institution is 51.4% (73/142) for all B3/B4 nodules (42.5% for

B3, 62.9% for B4). This value is higher than the 14–49% post-test probability of malignancy reported for B3/B4 Afirma-GEC-"suspicious" nodules [17–21]. Avoiding surgery after receiving suspicious results on molecular tests is challenging both for the physician and the patient. Thus, performing GEC analysis in all our patients with B3/B4 nodules and operating on all those with suspicious results would have possibly led to an increased number of unnecessary thyroidectomies. Accordingly, in a study by Roychoudhury et al. [18], 87% of the Afirma-suspicious nodules were resected, but pathology revealed malignant lesions in only 12% of them.

ThyroSeq is a multigene test for cytologically indeterminate thyroid nodules based on gene sequencing and mutational analysis of panels of genes involved in thyroid cancer. This "rule in" test is not available in Israel. However, postvalidation studies for the ThyroSeq version 2 showed a pooled positive predictive value (PPV) of 51.2% for thyroid cancer in B3/B4 thyroid nodules, similar to our PPV of 51.4% [22].

Recently, the Afirma test was switched from GEC to gene sequencing classifier (GSC) analysis, which was developed to improve the specificity and PPV while maintaining a good NPV. The GSC incorporates nuclear and mitochondrial RNA transcriptome gene expression, RNA sequencing, and genomic copy number analysis [23]. However, to date, only a few studies have compared the real-world clinical performance of the GSC with prior clinical experience with the GEC [24, 25]. ThyroSeq version 3 was released for clinical use in 2018 with a larger number of gene mutation hotspots and gene fusions analyzed and a reported PPV of 66% [26]. Analysis of postvalidation studies is currently unavailable.

During active surveillance, among the 174 patients in the B3 group, 64 (36.8%) had benign findings on repeated FNA after the index FNA performed in 2011–2012. A high rate of benign cytology on repeated FNA of B3 nodules has been documented in both intra- and inter-observer studies [4, 27, 28]. These data suggest that in patients with B3 nodules, molecular testing should be considered only if the cytology remains indeterminate on repeated FNA and/or in the event of high clinical suspicion of thyroid cancer when test findings would change the management.

Our cohort included 72 patients with B4 nodules, of whom 15 were not initially operated because of clinical considerations or patient preference. During surveillance, 5 patients were eventually operated, and in another 6, surgery was avoided for objective reasons. Alexander et al. [10] found no difference in the performance of GEC analysis between B3 and B4 lesions, with a similar prevalence of malignancy (24/25%), PPV (37/38%), and NPV (94/95%) [10]. By contrast, at our institution, the clinical significance and outcomes between B3 and B4 nodules were substantially different. While most patients with B3 nodules were not operated (68.4%), 86.1% of the patients with B4 nodules eventually underwent thyroidectomy. The preoperative ROM is 62.9% for our B4 subgroup, considerably higher than that reported by Alexander et al. [10]. Thus, given the current limitations of molecular testing in terms of price and accuracy, a different algorithm might be applied for its use in patients with B3 nodules and patients with B4 nodules. Accordingly, the high ROM associated with B4 cytology at our institution justifies thyroidectomy, skipping the need for molecular analysis in most patients. Nevertheless, we do not exclude the potential benefit of molecular testing in selected B4 nodules, like in patients with low clinical/sonographic suspicion for malignancy or patients at high surgical risk.

Our study has several strengths and limitations. A major strength is the significant amount of available clinical, imaging, and pathological data. Another important strength is the long follow-up period, with a median of 5 years. The main limitation of the study is its retrospective design with the associated risk of missing data. Additionally, our results reflect the cytological and clinical performance of our institution and may not be generalizable to other medical centers or community clinics.

In conclusion, our study of a large cohort of patients followed over a long term shows that in most cases, cytologically indeterminate thyroid nodules may be safely managed without molecular testing, provided the cytologists and clinicians in charge possess understanding and experience with this patient group. In the current era of rapidly evolving molecular diagnostic tests for malignancy, applying a myriad of clinical considerations beyond a single cytopathological report, and certainly before molecular analysis, is still the primary key for appropriate decision-making on an individual basis.

Statement of Ethics

The study protocol was approved by the Ethics Review Board of Rabin Medical Center. Informed consent was waived by the Ethics Committee due to the retrospective review-of-chart study design.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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No competing financial interests exist for any author.

Author Contributions

A.G., I.S.-S., E.R., C.B., and D.H. contributed to the design and implementation of the study, to data collection and analysis of the results, and to the writing of the manuscript. A.G. designed the Figure.

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