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Accuracy of fine-needle aspiration biopsy for predicting neoplasm or carcinoma in thyroid nodules 4 cm or larger

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Abstract

Hypothesis—All thyroid nodules ≥4 cm should be surgically removed regardless of fine-needle aspiration biopsy (FNAB) results due to an unacceptably high rate of false-negative pre-operative biopsies in these large nodules.

Design—Retrospective cohort study.

Setting—Single institution, tertiary academic referral center.

Patients and Methods—A retrospective analysis was done on all patients who underwent surgery for a thyroid nodule ≥4 cm from 5/94 through 1/07. Preoperative FNAB results were correlated with final surgical pathologic results. FNAB results were reported as non-diagnostic, benign, inconclusive (follicular neoplasm), or malignant while final surgical pathologic data was reported as benign or malignant.

Results—Of 155 patients who had a thyroidectomy for a ≥4cm nodule, 21 patients (14%) had clinically significant thyroid carcinoma within the ≥4cm nodule on final pathology. Preoperative cytology of the ≥4cm mass was obtained and read as benign in 52/97 patients, inconclusive in 23/97 patients, non-diagnostic in 11/97 patients, and malignant in 11/97 patients. In lesions ≥4cm, 26/52 (50%) FNAB results reported as benign turned out to be either neoplastic (22/52) or malignant (4/52) on final pathology. Among patients with non-diagnostic FNAB, the risk of malignancy was 27%.

Conclusions—In patients with thyroid nodules ≥4cm, FNAB results are highly inaccurate, misclassifying half of all patients with reportedly benign lesions on FNAB. Furthermore, those patients with a non-diagnostic FNAB display a very high risk of differentiated thyroid carcinoma. Therefore, we recommend that diagnostic lobectomy, at a minimum, be performed in patients with thyroid nodules ≥4 cm regardless of FNA cytology.

Background

Clinically apparent thyroid nodules are extremely common, affecting between 4 to 10% of the adult population in the United States[1, 2]. These figures likely underestimate the true frequency of thyroid nodular disease, as demonstrated by several autopsy surveys reporting rates of 37 to 57%[3, 4]. Likewise, in radiographic surveys of random subjects using ultrasonography, 20 to 76% of adult women were found to have at least one thyroid nodule[5, 6]. Despite this relative frequency, however, large retrospective case series have shown that only 4 to 5% of thyroid nodules demonstrate histopathologically proven malignancy[7, 8]. Several risk factors for the presence of carcinoma within thyroid nodules have been

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identified, including age, gender, and prior history of neck irradiation. Similarly, though controversial, the prevalence of thyroid carcinoma appears to be associated with larger thyroid nodule size [9, 10].

Fine-needle aspiration biopsy (FNAB) is an efficient and reliable means for the evaluation of thyroid nodules, and it has been shown to have a reported diagnostic sensitivity of 89 to 98% and specificity of 92%[9, 11–13]. As such, FNAB has become the primary diagnostic procedure in diagnosing thyroid malignancy and in guiding the surgical management of patients with FNAB-proven carcinoma. Unfortunately, the diagnostic accuracy of FNAB has been shown to be limited in large thyroid nodules [9, 10, 14, 15]. In a retrospective case review of 90 patients who underwent FNAB followed by thyroidectomy, Meko and Norton [15] noted a false-negative rate of 17% in patients with large (3cm or larger) thyroid nodules; with the addition of cystic/solid architecture, the false-negative rate approached 30%. Carrillo and colleagues [10] confirmed the importance of nodule size in a prospective study of 159 patients who underwent thyroid surgery following FNAB evaluation, concluding that the only clinical factor associated with false-negative FNAB results in patients with indeterminate FNAB was size ≥4cm. More recently, McCoy and colleagues[9] noted that preoperative FNAB results in patients with thyroid nodules ≥4cm were read incorrectly as benign in 13% of patients with cancer; when multifocal micropapillary carcinoma was included, this false-negative rate for preoperative FNAB reached 16%.

Though it has recently been shown that the diagnostic accuracy of surgeon-performed ultrasound-guided thyroid FNAB may result in less sampling error and fewer false-negative FNAB results in patients with thyroid nodules[12], there remains little consensus on the actual rate of false-negative FNABs in patients with large thyroid nodules. In this study, we present data from a large, prospective database of patients who underwent thyroid surgery after FNAB for thyroid nodules ≥4cm.

Methods

Data Acquisition and Patient Selection

After obtaining approval from the University of Wisconsin Institutional Review Board, the authors reviewed a prospective, single-institution operative database of 155 consecutive patients who underwent thyroid surgery for a thyroid nodule ≥4 cm from May 1994 to January 2007. Preoperative cytology of the ≥4cm nodule was retrospectively identified and analyzed in 97 of these 155 patients, essentially identifying the cohort for this study. Patients with a prior history of thyroid surgery or thyroid carcinoma were excluded from the study. Nodule size was determined based on final surgical pathology. In patients with a multinodular goiter, histopathology of the dominant nodule (nodule with the largest diameter) was utilized. In all patients, cytopathologic, operative, and histopathologic findings were reviewed. Preoperative indications for thyroid surgery included a nodule exceeding 4 cm, compressive symptoms, or preoperative cytology consistent with thyroid carcinoma, follicular neoplasm, or non-diagnostic FNAB; however, thyroid nodule size exceeding 4 cm was not an independent indication for thyroidectomy in this study.

FNAB Technique

In the first half of the study (1994–2000), FNAB was used selectively in the patient population. Every patient with a palpable thyroid nodule was a candidate for FNAB and underwent further evaluation, including a serum thyrotropin (TSH) level[16] and thyroid ultrasound (US), to determine whether FNAB was warranted. Likewise, patients with thyroid nodules discovered via imaging were candidates for FNAB if the nodule possessed suspicious features—nodules exceeding 1cm in greatest diameter or sonographic

microcalcifications, for example—by imaging standards. Although the majority of FNABs were done with palpation-guidance in this period, US-guided FNAB was utilized and was the preferred technique for nodules that were not palpable, were largely cystic, or had been previously biopsied with a non-diagnostic result. Since 2000, our standard of care has changed to include US-guidance for FNAB of the thyroid nodule. Likewise, FNAB has become standard in the work-up of all patients with large thyroid nodules. At the study institution, the majority of thyroid aspirations were performed by clinicians and were not always attended by a pathologist.

FNAB Cytopathology and Histopathologic Definitions

FNAB cytopathology results were stratified into the following categories: non-diagnostic, benign, inconclusive, or malignant. Thyroid FNAB was reported as non-diagnostic when there were too few or absent follicular cells and an interpretation was not possible. A report containing the diagnosis “benign,” “goiter,” “cyst,” “adenoma,” or “no evidence of malignancy” was recorded as benign. Inconclusive FNABs included those described as “indeterminate” or those labeled “suspicious for follicular neoplasm,” “suspicious for Hürthle cell neoplasm,” or “atypical cytologic features suggestive of follicular neoplasm.” FNABs read by the pathologist as unequivocally malignant were coded as malignant. All FNAB results were reviewed by a dedicated endocrine cytopathologist.

Permanent pathologic diagnoses were recorded as malignant for any report of papillary thyroid cancer (PTC), medullary thyroid cancer (MTC), or follicular (FTC), Hürthle cell (HCC), or anaplastic thyroid carcinoma. Histopathologic evidence of metastases to the thyroid, lymphoma, and squamous cell carcinoma of the thyroid were also recorded as malignant. A size cutoff of 1cm was utilized to differentiate true PTC from micropapillary thyroid carcinoma. For purposes of this study, clinically significant thyroid carcinoma included all malignancies greater than 1cm in size. Benign lesions were reported as follicular cell adenoma, Hürthle cell adenoma, nodular goiter, thyroiditis, or simple cyst.

Statistical Analysis

Continuous variables were analyzed utilizing the Student’s *t* test to compare two means, whereas categorical data were compared with Fisher’s and chi-square analysis where appropriate. A P value of ≤ 0.05 was considered significant.

Results

Of the 155 patients who underwent thyroid surgery for a dominant thyroid nodule ≥4 cm, 132 (85%) were found to have benign final pathology and 21 patients (14%) had a final histopathologic diagnosis of clinically significant thyroid carcinoma. An additional 2 patients (1%) had a single focus of micropapillary thyroid carcinoma within the dominant thyroid nodule. There were no patients with foci of micropapillary thyroid carcinoma documented outside of the dominant ≥4 cm nodule. The characteristics of the study patients, grouped by final pathologic diagnosis, are outlined in Table I. As shown on final pathology, the individual nodules were found to range from 4 to 20 cm in greatest dimension, but there was no statistical difference between nodules with benign or malignant histopathology. The female-to-male ratio was approximately 2.3:1 and the average age of the patients was 53 years. Patients with a final histopathologic diagnosis of cancer were significantly older (61 years vs. 52 years, $P<.05$) than patients with benign pathology.

Although previous studies have demonstrated an association of thyroid cancer with lymphocytic thyroiditis (LT)[9], there was no statistically significant association with LT in our study population. LT was present pathologically in 23 patients overall (Table I). Of

these 23 patients, 3 (13%) were found to have a clinically significant thyroid cancer while no patients LT had a micropapillary thyroid carcinoma. Of patients without LT, 18/132 (13.6%) had clinically significant carcinoma (*P*=1.000), suggesting no association between LT and clinically significant thyroid caner. A total of 51 patients (33%) were found to have a multinodular goiter (MNG) on final surgical pathology. In patients with MNG, the presence of a dominant nodule exceeding 4 cm in diameter or compressive symptoms were the indications for operative therapy. Of these, 50/51 (98%) goiters did not contain any foci of carcinoma, while one goiter contained a focus of MTC in a 5 cm dominant nodule (Table I).

Of the 155 patients who underwent thyroid surgery for a nodule ≥4cm, 97 patients (62.5%) had preoperative FNAB and 58 did not. The preoperative cytopathology and final surgical pathology results for these patients are described in Table II. Preoperative cytology of the ≥4cm mass was obtained and read as benign in 52/97 patients, inconclusive in 23/97 patients, non-diagnostic in 11/97 patients, and malignant in 11/97 patients. Though the preoperative cytology was benign in 52 of 97 (54%) patients, in 3 of 52 cases the thyroid nodule identified as benign proved to harbor a clinically significant thyroid carcinoma. This represents a false-negative rate for benign cytology of the dominant nodule of nearly 6%. Additionally, 1 of 52 (2%) thyroid nodules identified as benign contained a single focus of micropapillary thyroid carcinoma within the dominant thyroid nodule, increasing the false-negative rate to approximately 8%. Final surgical pathology for these 4 cancers is outlined in Table III, and included 3 cases of PTC >10mm and one micropapillary PTC. Interestingly, 18 of 52 (34.6%) patients with benign preoperative FNAB results ended up having a follicular adenoma on final surgical pathology, while an additional 4 patients (7.7%) had a Hürthle cell adenoma on final surgical pathology. As such, in lesions ≥4cm, 26 of 52 (50%) FNAB results reported as benign turned out to be either neoplastic or malignant on final pathology (Table III).

Pre-operative cytologic findings classified as non-diagnostic, commonly a clinical dilemma among practicing clinicians, demonstrated interesting patterns as well. Of the 11 patients with non-diagnostic FNABs, 2 (18.2%) patients had clinically significant PTC or HCC on final histopathologic examination of the dominant nodule, while 1 (9%) nodule contained a micropapillary thyroid carcinoma. This represents a malignancy rate of nearly 27% for non-diagnostic cytology. Likewise, nearly 50% of patients with non-diagnostic FNAB cytology harbored a follicular adenoma (5/11 patients) within the dominant thyroid nodule. It should be noted that in this study, all patients in non-diagnostic cytology group did not undergo repeated FNAB attempts; rather, all of these patients proceeded directly to surgery due to compressive symptoms or suspicious imaging characteristics of the dominant thyroid nodule.

Comments

While nodular disease of the thyroid gland is prevalent in the United States—the lifetime risk for developing a palpable thyroid nodule is estimated to be 5–10%—malignancy of the thyroid nodule is rare in the American population, occurring in only 5% of all nodules[14]. Several studies support the emergence of FNAB as a sensitive and specific test for the diagnosis of thyroid cancer, allowing definitive initial surgery and avoiding unnecessary procedures [9, 12, 13]. In a recent series of nearly 450 consecutive patients who underwent thyroid surgery for an index nodule, Greenblatt and colleagues[13] demonstrated that nearly 98% of patients with clinically significant thyroid carcinoma or thyroid lymphoma received optimal surgical treatment—defined as no need for completion thyroidectomy for PTC and MTC and as no unnecessary surgery for lymphoma—when FNAB was performed versus no pre-operative FNAB.

Although FNAB of thyroid nodules has been established as an important tool for the diagnosis of thyroid cancer, the procedure is not without limitations. Due to a relatively high sensitivity—reported as 89 to 98% in some studies[9, 13, 14, 17, 18]—a positive FNAB result for malignancy translates to a positive predictive value of the test that approaches 100%[10]. Conversely, in the presence of a negative result, this value decreases significantly. As such, researchers have stressed the importance of critically evaluating co-existent clinical factors in the diagnostic process that may improve the detection of malignant pathology in patients with thyroid nodular disease.

Preoperative FNAB cytology has been shown to be highly inaccurate in larger thyroid nodules[9, 14, 15], a subset of thyroid nodules thought to be associated with a higher prevalence of malignancy[19]. In a study of clinical factors associated with true-negative results and the factors corresponding to false-negative results, Carrillo and coleagues[10] echoed previous studies when they demonstrated a significantly greater frequency of false-negative pre-operative biopsies on the order of 10 to 20%. Just recently, McCoy et al[9] addressed this important issue, citing a false-negative rate of FNAB approximating 16% in a large retrospective series of 223 patients. Despite these convincing data, however, no general consensus exists among endocrinologists and surgeons regarding the optimal management of these patients with large thyroid nodules.

In this study, our data show that in patients with thyroid nodules ≥4cm, FNAB results are highly inaccurate, misclassifying half of all patients with reportedly benign lesions on FNAB. In our study of 155 patients with thyroid nodules ≥4cm, 97 (62.5%) patients had both preoperative FNAB cytopathology and postoperative histopathology available. Three patients were found to have clinically significant PTC in a thyroid nodule deemed “benign” by pre-operative FNAB evaluation while one additional patient was shown to have a micropapillary thyroid carcinoma within a FNAB-defined “benign” nodule. This represents a false-negative rate of approximately 8%.

Perhaps more worrisome, our study additionally demonstrated a high rate of missed follicular lesions (thyroid nodules read as benign which were later found to harbor follicular architecture on final histopathologic evaluation). Typically, aspirates demonstrating high follicular cellularity suggest follicular neoplasm; however, FNAB cannot be used reliably to distinguish a benign follicular neoplasm from a malignant neoplasm, prompting at least a diagnostic lobectomy for determination of malignancy within the nodule. Our study found an alarmingly high rate of missed follicular lesions in 22 of 52 (42%) thyroid nodules which, when combined with false-negative FNAB results in this study, essentially misclassifies half of all patients with reportedly benign lesions. Surprisingly, none of the patients with a missed follicular lesion had a malignant follicular neoplasm; however, FNAB misclassified these lesions from an inconclusive category, which would have led to surgical resection, to a benign category, which were followed clinically by close observation alone.

Despite these data, several recent abstracts (data unpublished) have suggested that increasing nodule size is not predictive of thyroid malignancy and should not be used in lieu of FNAB for therapeutic decision making. Similarly, some researchers believe benign diagnoses of thyroid nodules ≥3cm by US-guided FNAB (data unpublished) are highly reliable with demonstrated false-negative rates of less than 1%. Though we certainly feel that the use of US-guided FNAB has decreased sampling error of FNAB significantly, we maintain that the false-negative rates of FNAB are much higher than these recent studies, as demonstrated by our data and that of others[9, 20, 21].

We found that patients with MNG rarely harbored a thyroid carcinoma. In a retrospective observational cohort study of nearly 2000 patients with one or more nodules larger than

10mm, Frates and colleagues [22] demonstrated that the likelihood of thyroid cancer per patient is independent of the number of nodules, whereas the likelihood per nodule decreases as the number of nodules increases. Additionally, their data showed the prevalence of thyroid carcinoma in patients with multiple nodules to be 14.9%[22]. In our study, of 51 total patients with a ≥4 cm thyroid nodule in the setting of MNG, only one patient (1.9%) was found to have a differentiated thyroid carcinoma on final histopathologic examination of the surgical specimen in which all nodules within the specimen are evaluated. Our rate of clinically significant thyroid cancer is significantly lower than previously published reports. The authors acknowledge this rate of carcinoma may be falsely depressed based on selection bias; that is, patients with FNAB-proven benign dominant nodules may have only had a thyroid lobectomy for compressive symptoms rather than a total thyroidectomy. We acknowledge that the nodules which remained in vivo may harbor clinically significant carcinoma or micropapillary carcinoma.

Though MNG was not found to be significantly associated with malignancy in our study, several clinical factors were identified which may be associated with higher rates of malignant pathology within thyroid nodules ≥4 cm. Rates of thyroid carcinoma on final histopathologic evaluation were statistically higher in older, male patients with large thyroid nodules. The mean age of patients with clinically significant thyroid cancer in this study was 61 ± 3.8 years versus 52 ± 1.3 years ($P<0.05$) in those patients with benign pathology. Likewise, the malignant group was predominantly male compared to the benign group (62% vs. 26% male, $P<0.05$). These data clearly support the multitude of clinicopathologic staging systems for differentiated thyroid cancer, most of which include increased patient age as an independent prognostic variable for the prediction of thyroid cancer[23–25]. Similarly, these data support Machens and colleagues[26] research, which demonstrated larger tumor sizes and a higher prevalence of lymph node metastases, extra-thyroidal extension, and distant metastases in male patients with sporadic thyroid carcinomas versus female patients.

There was no clear association between thyroid cancer and LT; in fact, 20 of 132 (15.2%) patients with benign pathology had coexistent LT, while 3 of 21 (14.3%) patients with cancer also had LT. Obviously, while these differences are not statistically significant, the coexistence of LT and PTC in our study compares with previously reported rates in the literature of 0.5% to 32%[9].

In conclusion, while most of the errors in FNAB are likely related to sampling error or mistaken cytologic interpretation, improvements in technique and technologic advances in imaging for FNAB will likely reduce the percentage of suspicious and false-negative FNAB results in this cohort with large thyroid nodules. Our data calls into question the diagnostic accuracy of a reportedly benign FNAB of a thyroid nodule exceeding 4cm. While the rate of false-negative FNABs in this study is similar to those which have been previously published (6%), the high rate of missed follicular lesions in patients with reportedly benign FNABs is alarming. Missing these diagnoses of follicular neoplasms is potentially worrisome due to the fact that the clinical management of follicular cytology (diagnostic lobectomy) is significantly different than that for true benign cytology (observation). Therefore, though we support the use of FNAB in the confirmation of thyroid malignancy, a negative FNAB result in this cohort prompts us to recommend that diagnostic lobectomy, at a minimum, be performed in patients with thyroid nodules ≥4 cm regardless of FNA cytology.

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Table I

General clinical characteristics of the study patients

	Pathology Finding			
	Benign	**Carcinoma**	**mPTC†**	**Total**
n	132	21	2	155
Age				
Mean (yr)	52 ± 1.3	61 ± 3.8*	56 ± 7.7	53 ± 1.3
Range (yr)	7–89	32–86	49–64	7–89
Gender				
Male	34	13*	0	47
Female	98	8	2	108
Nodule size				
Mean (cm)	5.5 ± 0.2	5.4 ± 0.3	5.4 ± 0.9	5.5 ± 0.2
Range (cm)	4.0–20.0	4.0–10.0	4.5–6.3	4.0–20.0
LT	20/132 (15.2%)	3/21 (14.3%)	0/2 (0%)	23/155 (14.8%)
MNG	50/132 (37.9%)	1/21 (4.7%)*	0/2 (0%)	51/155 (32.9%)

LT, lymphocytic thyroiditis on final pathology; MNG, multinodular goiter on final pathology; mPTC, micropapillary thyroid carcinoma

† mPTC=papillary thyroid carcinoma < 10mm

* $p<0.05$

Table II

Distribution of cytology and pathology results of 97 of 155 patients with pre-operative FNAB

	Pathology Finding			
FNAB Result	**Benign**	**Carcinoma**	**mPTC†**	**Total**
Benign	48 (92.3%)	3 (5.8%)	1 (1.9%)	52
Inconclusive (Follicular Lesion)	19 (82.6%)	4 (17.4%)	0	23
Malignant	1 (9%)	10 (91%)	0	11
Nondiagnostic	7 (63.6%)	3 (27.3)	1 (9.1%)	11

† mPTC=papillary thyroid carcinoma < 10mm

Table III

Final histopathology of all FNAB cytology subdivisions

	Preoperative FNAB Cytology			
Final Diagnosis	**Benign**	**Inconclusive**	**Malignant**	**Non-diagnostic**
n	52	23	11	11
Carcinoma (%)				
PTC	4 (7.7%)	1 (4.3%)	8 (72.7%)	2 (18.2%)
FC	0	1 (4.3%)	0	0
HCC	0	2 (8.7%)	0	1 (9.1%)
MTC	0	0	1 (9.1%)	0
Anaplastic	0	0	1 (9.1%)	0
Benign follicular neoplasm (%)				
FA	18 (34.6%)	13 (56.6%)	0	5 (45.4%)
HCA	4 (7.7%)	3 (13.1%)	0	0
Benign pathology (%)				
MNG	17 (32.7%)	2 (8.7%)	0	1 (9.1%)
Benign nodule/cyst	9 (17.3%)	1 (4.3%)	0	2 (18.2%)
Sarcoid/noncaseating granuloma	0	0	1 (9.1%)	0

PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hürthle cell carcinoma; MTC, medullary thyroid carcinoma; FA, follicular adenoma; HCA, Hürthle cell carcinoma; MNG, multinodular gouter