Accuracy of Fine-Needle Aspiration Biopsy for Predicting Neoplasm or Carcinoma in Thyroid Nodules 4 cm or Larger

Scott N. Pinchot, MD; Hatem Al-Wagih, MD; Sarah Schaefer, NP; Rebecca Sippel, MD; Herbert Chen, MD

Hypothesis: All thyroid nodules 4 cm or larger should be surgically removed regardless of fine-needle aspiration biopsy (FNAB) results because of an unacceptably high rate of false-negative preoperative biopsy results in these large nodules.

Design: Retrospective cohort study.

Setting: Single-institution, tertiary academic referral center.

Patients: A retrospective analysis was performed on all patients who underwent surgery for a thyroid nodule 4 cm or larger from May 1, 1994, through January 31, 2007.

Main Outcome Measures: Preoperative FNAB results were correlated with final surgical pathologic results. The FNAB results were reported as nondiagnostic, benign, inconclusive (follicular neoplasm), or malignant, whereas the final surgical pathologic data were reported as benign or malignant.

Results: Of 155 patients who underwent a thyroidectomy for a nodule 4 cm or larger, 21 patients (13.5%) had a clinically significant thyroid carcinoma within the nodule on final pathologic analysis. Preoperative cytologic testing of the mass was performed on 97 patients, and the results read as benign for 52, inconclusive for 23, nondiagnostic for 11, and malignant for 11. In lesions 4 cm or larger, 26 of 52 FNAB results reported as benign (50.0%) turned out to be either neoplastic (22) or malignant (4) on final pathologic analysis. Among patients with nondiagnostic FNAB results, the risk of malignant neoplasms was 27.3%.

Conclusions: In patients with thyroid nodules 4 cm or larger, the FNAB results are highly inaccurate, misclassifying half of all patients with reportedly benign lesions. Furthermore, those patients with a nondiagnostic FNAB result display a high risk of differentiated thyroid carcinoma. Therefore, we recommend that diagnostic lobectomy be strongly considered in patients with thyroid nodules 4 cm or larger regardless of FNAB cytologic test results.

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Clinically apparent thyroid nodules are extremely common, affecting 4% to 10% of the adult population in the United States. These figures likely underestimate the true frequency of thyroid nodular disease, as demonstrated by several autopsy surveys reporting rates of 37% to 57%. Likewise, in radiographic surveys of random patients undergoing ultrasonography, 20% to 76% of adult women were found to have at least 1 thyroid nodule. Despite this relative frequency, large retrospective case series have shown that only 4% to 5% of thyroid nodules demonstrate histopathologically proven malignant disease. Several risk factors for the presence of carcinoma within thyroid nodules have been identified, including age, sex, and prior neck irradiation. Similarly, although controversial, the prevalence of thyroid carcinoma appears to be associated with larger thyroid nodule size.

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 diagnostic sensitivity of 89% to 98% and a specificity of 92%. As such, FNAB has become the primary procedure for diagnosing thyroid malignant neoplasms and guiding the surgical treatment of patients with FNAB-proven carcinoma. Unfortunately, the diagnostic accuracy of FNAB has been shown to be limited in large thyroid nodules. In a retrospective case review of 90 patients who underwent FNAB followed by thyroidectomy, Meko and Norton noted a false-negative rate of 17% in patients with large (≥3 cm) thyroid nodules.
ules; with the addition of cystic or solid architecture, the false-negative rate approached 30%. Carrillo and colleagues confirmed the importance of nodule size in a prospective study of 159 patients who underwent thyroid surgery after FNAB evaluation, concluding that the only clinical factor associated with false-negative FNAB results in patients with indeterminate FNAB was size of 4 cm or larger. More recently, McCoy and colleagues noted that preoperative FNAB results in patients with thyroid nodules 4 cm or larger 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%

Although it has recently been shown that the diagnostic accuracy of surgeon-performed ultrasonography-guided thyroid FNAB may result in less sampling error and fewer false-negative FNAB results in patients with thyroid nodules, little consensus remains on the actual rate of false-negative FNAB results 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 solitary or dominant thyroid nodules 4 cm or larger.

DATA ACQUISITION AND PATIENT SELECTION

After obtaining approval from the University of Wisconsin, Madison institutional review board, we reviewed a prospective, single-institution operative database of 155 consecutive patients who underwent thyroid surgery for a thyroid nodule 4 cm or larger from May 1, 1994, to January 31, 2007. Preoperative cytologic test reports of the nodules were obtained in 97 of these 155 patients, essentially identifying a subset of the population studied in whom preoperative FNAB cytologic test results could be corroborated with final surgical pathologic test results. Patients with a family history of thyroid carcinoma, documented evidence of multiple endocrine neoplasia syndrome, or a history of thyroid surgery or thyroid carcinoma were excluded from the study. Nodule size was determined based on final surgical pathologic test results. In patients with a multinodular goiter, the largest thyroid nodule was used. In all patients, FNAB was performed with palpation guidance in this period, ultrasonography-guided FNAB was used and was the preferred technique for nodules that were not palpable, were largely cystic or complex, or had been previously biopsied with a non-diagnostic result. Since 2000, our standard of care has changed to include ultrasonography guidance for FNAB of the thyroid nodule. Likewise, FNAB has become standard in the workup of all patients with large thyroid nodules. At the study institution, most thyroid aspirations were performed by physicians and were not always attended by a pathologist.

FNAB TECHNIQUE

In the first half of the study (May 1, 1994, to January 1, 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 serum thyrotropin measurement and thyroid ultrasonography, to determine whether FNAB was warranted. Likewise, patients with thyroid nodules discovered via imaging were candidates for FNAB if the nodule possessed features suggestive of disease (eg, nodules exceeding 1 cm in greatest diameter or sonographic microcalcifications) by imaging standards. Although most FNABs were performed with palpation guidance in this period, ultrasonography-guided FNAB was used and was the preferred technique for nodules that were not palpable, were largely cystic or complex, or had been previously biopsied with a non-diagnostic result. Since 2000, our standard of care has changed to include ultrasonography guidance for FNAB of the thyroid nodule. Likewise, FNAB has become standard in the workup of all patients with large thyroid nodules. At the study institution, most thyroid aspirations were performed by physicians and were not always attended by a pathologist.
logic test results for these patients are given in preoperative cytopathologic and final surgical pathology. Of the 155 patients who underwent thyroid surgery for a nodule 4 cm or larger, 97 patients (62.5%) underwent preoperative FNAB and 58 (37.4%) did not. The sensitivity and specificity of FNAB for detecting thyroid carcinoma before January 2000 was 100% and 97%, respectively, for FNABs performed after January 2000; the Abbreviation: mPTC, micropapillary thyroid carcinoma (≤10 mm).

Table 1. General Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Benign (n=132)</th>
<th>Carcinoma (n=21)</th>
<th>mPTC (n=2)</th>
<th>Total (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>52 (1.3) [7-89]</td>
<td>61 (3.8) [32-86]</td>
<td>56 (7.7) [49-64]</td>
<td>53 (1.3) [7-89]</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>34/98</td>
<td>13/8</td>
<td>0/2</td>
<td>47/108</td>
</tr>
<tr>
<td>Nodule size, mean (SD) [range], cm</td>
<td>5.5 (0.2) [4.0-20.0]</td>
<td>5.4 (0.3) [4.0-10.0]</td>
<td>5.4 (0.9) [4.5-6.3]</td>
<td>5.5 (0.2) [4.0-20.0]</td>
</tr>
</tbody>
</table>

Abbreviation: mPTC, micropapillary thyroid carcinoma (<10 mm).

Table 2. Lymphocytic Thyroiditis and Multinodular Goiter Prevalence in Benign and Malignant Histopathologic Groups

<table>
<thead>
<tr>
<th>Pathologic Test Findings</th>
<th>Benign (n=132)</th>
<th>Carcinoma (n=21)</th>
<th>mPTC (n=2)</th>
<th>Total (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic thyroiditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20 (15.2)</td>
<td>3 (14)</td>
<td>0</td>
<td>23 (14.8)</td>
</tr>
<tr>
<td>Absent</td>
<td>112 (84.8)</td>
<td>18 (86)</td>
<td>2 (100)</td>
<td>132 (85.2)</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>50 (37.9)</td>
<td>1 (5)</td>
<td>0</td>
<td>51 (32.9)</td>
</tr>
<tr>
<td>Absent</td>
<td>82 (62.1)</td>
<td>20 (95)</td>
<td>2 (100)</td>
<td>104 (67.1)</td>
</tr>
</tbody>
</table>

Abbreviation: mPTC, micropapillary thyroid carcinoma (<10 mm).

individual nodules were found to range from 4.0 to 20.0 cm in greatest dimension, but no statistical difference was found between nodules with benign or malignant histopathologic test results. 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 vs 52 years; P=0.01) than patients with benign pathologic test results.

Although previous studies have demonstrated an association of thyroid cancer with lymphocytic thyroiditis (LT), no statistically significant association was found with LT in our study population. We found that LT was present pathologically in 23 patients overall (Table 2). Of these 23 patients, 3 (13%) were found to have a clinically significant thyroid cancer, whereas no patients with LT had an mPTC. Of patients without LT, 18 of 132 (13.6%) had clinically significant carcinoma (P>0.99), suggesting no association between LT and clinically significant thyroid cancer. A total of 51 patients (32.9%) were found to have an MNG on final surgical pathologic analysis. 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 of 51 goiters (98%) did not contain any foci of carcinoma, whereas 1 goiter contained a focus of MTC in a 5-cm dominant nodule (Table 2).

Of the 155 patients who underwent thyroid surgery for a nodule 4 cm or larger, 97 patients (62.5%) underwent preoperative FNAB and 58 (37.4%) did not. The preoperative cytologic and final surgical pathologic test results for these patients are given in Table 3. Preoperative cytologic testing of the mass 4 cm or larger was performed in 97 patients and the results read as benign in 52, inconclusive in 23, nondiagnostic in 11, and malignant in 11. Although the preoperative cytologic test result was benign in 52 of 97 patients (54%), in 3 of 52 patients the thyroid nodule identified as benign proved to harbor a clinically significant thyroid carcinoma. This finding represents a false-negative rate for benign cytologic test results of the dominant nodule of nearly 6%. In addition, 1 of 52 thyroid nodules (2%) identified as benign contained a single focus of mPTC within the dominant thyroid nodule, increasing the false-negative rate to approximately 8%. Final surgical pathologic results for these 4 cancers are outlined in Table 3 and included 3 cases of PTC larger than 10 mm and 1 mPTC. Interestingly, all FNABs with false-negative results were performed after 2000, when ultrasonography-guided FNAB was routinely used in all patients. This resulted in a reported sensitivity and specificity of 67% and 100%, respectively, for FNABs performed after January 2000; the sensitivity and specificity of FNAB for detecting thyroid carcinoma before January 2000 was 100% and 97%, respectively. Among patients with benign preoperative FNAB results, 18 of 52 (35%) patients ended up having a follicular adenoma on final surgical pathologic testing, whereas an additional 4 patients (8%) had a Hurthle cell adenoma on final surgical pathologic testing. As such, in lesions 4 cm or larger, 26 of 52 FNAB results (50%) reported as benign turned out to be either neoplastic or malignant on final pathologic testing (Table 3).

Among 11 patients with nondiagnostic FNAB results, 2 (18%) had clinically significant PTC or HCC on final histopathologic examination of the dominant nodule, whereas 1 nodule (9%) contained an mPTC. This finding represents a malignancy rate of nearly 27% for
Table 3. Final Histopathologic Test Results of All FNAB Cytologic Subdivisions

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Preoperative FNAB Cytologic Test Results, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign (n=52)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>PTC</td>
<td>3 (6)</td>
</tr>
<tr>
<td>mPTC</td>
<td>1 (2)</td>
</tr>
<tr>
<td>FTC</td>
<td>0</td>
</tr>
<tr>
<td>HCC</td>
<td>0</td>
</tr>
<tr>
<td>MTC</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>0</td>
</tr>
<tr>
<td>Benign follicular neoplasm</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>18 (35)</td>
</tr>
<tr>
<td>HCA</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Benign disease</td>
<td></td>
</tr>
<tr>
<td>MNG</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Benign nodule or cyst</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Sarcoma or noncaseating granuloma</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: FA, follicular adenoma; FNAB, fine-needle aspiration biopsy; FTC, follicular thyroid carcinoma; HCA, Hürthle cell adenocarcinoma; HCC, Hürthle cell carcinoma; MNG, multinodular goiter; mPTC, micropapillary thyroid cancer (<10 mm); MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

nondiagnostic cytologic testing. Likewise, nearly 50% of patients with nondiagnostic FNAB cytologic test results harbored a follicular adenoma (5 of 11 patients) within the dominant thyroid nodule. In this study, all patients with nondiagnostic cytologic test results did not undergo subsequent FNAB attempts; rather, all of these patients proceeded directly to surgery because of compressive symptoms or suspicious imaging characteristics of the dominant thyroid nodule.

Although 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 US population, occurring in only 5% of all nodules. 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. In a recent series of nearly 450 consecutive patients who underwent thyroid surgery for an index nodule, Greenblatt and colleagues 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 vs no preoperative 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. Because of a relatively high sensitivity (reported as 89% to 98% in some studies), a positive FNAB result for a malignant neoplasm translates to a positive predictive value of the test that approaches 100%. Conversely, in the presence of a negative result, this value decreases significantly. As such, researchers have stressed the importance of critically evaluating coexistent clinical factors in the diagnostic process that may improve the detection of malignant tumors in patients with thyroid nodular disease.

Preoperative FNAB cytologic testing has been shown to be highly inaccurate in larger thyroid nodules, a subset of thyroid nodules thought to be associated with a higher prevalence of malignant disease. In a study of clinical factors associated with true-negative results and the factors corresponding to false-negative results, Carrillo and colleagues echoed previous studies when they demonstrated a significantly greater frequency of false-negative preoperative biopsy results on the order of 10% to 20%. Just recently, McCoy et al 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 treatment of these patients with large thyroid nodules.

In this study, our data show that in patients with thyroid nodules 4 cm or larger, FNAB results are highly inaccurate, misclassifying half of all patients with reportedly benign lesions on FNAB specimens. In our study of 155 patients with thyroid nodules 4 cm or larger, 97 patients (62.5%) had both preoperative FNAB cytopathologic and postoperative histopathologic test results available. Three patients were found to have clinically significant PTC in a thyroid nodule deemed “benign” by preoperative FNAB evaluation, whereas 1 additional patient was shown to have a mPTC within an FNAB-defined “benign” nodule. This represents a false-negative rate of approximately 8%.

Perhaps more worrisome, our study also demonstrated a high rate of missed follicular lesions (thyroid nodules read as benign that 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 follicu-
ular neoplasm from a malignant neoplasm, prompting at least a diagnostic lobectomy for determination of malignancy within the nodule. Our study found a high rate of missed follicular lesions in 22 of 52 thyroid nodules (42%), which, when combined with false-negative FNAB results in this study, essentially misclassifies half of all patients with reportedly benign lesions. These data clearly support those of McCoy and colleagues,8 in which the false-negative rate with follicular and Hürthle cell neoplasms was 27% and the combined false-negative rate with carcinoma was 42%. 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, and as such, they were followed up clinically by close observation alone.

Despite these data, several recent abstracts20 have suggested that increasing nodule size is predictive of thyroid malignant neoplasms and should not be used in lieu of FNAB for therapeutic decision making. Similarly, some researchers21 believe benign diagnoses of thyroid nodules 3 cm or larger by ultrasonography-guided FNAB are highly reliable, with demonstrated false-negative rates of less than 1%. Although we certainly feel that the use of ultrasonography-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 those of others.8,22,23

In this study, when the cytologic specimen was interpreted as nondiagnostic (inadequate), the malignancy rate in patients was 27% (3/11). Certainly, this malignancy rate for nondiagnostic cytologic test results exceeds previously published rates of 8% to 10%. Analysis of these 3 patients revealed that each had undergone FNAB of the thyroid nodule before 1998; likewise, each FNAB was performed by palpation guidance only and was performed just once. The final histopathologic diagnoses of these 3 patients included 1 mPTC, 1 PTC, and 1 HCC. It is likely that a combination of sampling error (missed mPTC by palpation-guided FNAB) and lack of ultrasonography guidance resulted in misclassification of disease in these patients.

Similarly, it is unusual to have false-positive results with FNAB. In this study, a patient with isolated sarcoidosis of the thyroid gland was initially erroneously diagnosed as having carcinoma based on FNAB cytologic test results. Hyperthyroidism, subacute or Hashimoto disease, and papillary cancer have been reported to be associated with systemic sarcoidosis, but isolated involvement of the thyroid gland is rare. To our knowledge, to date, only 3 such case reports of this unusual presentation have been described in the English-language literature.

We found that patients with MNG rarely harbored a thyroid carcinoma. In a retrospective observational cohort study of nearly 2000 patients with 1 or more nodules larger than 10 mm, Frates and colleagues24 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. In addition, their data showed the prevalence of thyroid carcinoma in patients with multiple nodules to be 14.9%.24 In our study, of 51 total patients with a thyroid nodule 4 cm or larger who had MNG, only 1 patient (2%) 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 nodule that remained in vivo may harbor clinically significant carcinoma or micropapillary carcinoma.

Although MNG was not found to be significantly associated with malignant disease in our study, several clinical factors were identified that may be associated with higher rates of malignant disease within thyroid nodules 4 cm or larger. Rates of thyroid carcinoma on final histopathologic evaluation were statistically higher in older, male patients with large thyroid nodules. The mean (SEM) age of patients with clinically significant thyroid cancer in this study was 61 (3.8) years vs 52 (1.3) years (P = .01) in those patients with benign disease. Likewise, the malignant disease group was predominantly male compared with the benign group (62% vs 26% male; P = .001). 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.25-27 Similarly, these data support the research by Machens and colleagues,28 which demonstrated larger tumor sizes and a higher prevalence of lymph node metastases, extrathyroidal extension, and distant metastases in male patients with sporadic thyroid carcinomas vs female patients.

No clear association was found between thyroid cancer and LT; in fact, 20 of 132 patients (15.2%) with benign disease had coexistent LT, whereas 3 of 21 patients (14%) with cancer also had LT. Obviously, although 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, although most of the errors in FNAB are likely related to sampling error or mistaken cytologic test result 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 call into question the diagnostic accuracy of a reportedly benign FNAB result of a thyroid nodule larger than 4 cm. Although the rate of false-negative FNAB results in this study is similar to those that have been previously published (6%), the high rate of missed follicular lesions in patients with reportedly benign FNAB results is alarming. Missing these diagnoses of follicular neoplasms is potentially worrisome because the clinical management of follicular cytologic disease (diagnostic lobectomy) is significantly different from that for true benign cytologic disease (observation). There-
fore, although we support the use of FNAB in the confirmation of thyroid malignant neoplasms, a negative FNAB result in this cohort prompts us to recommend that diagnostic lobectomy be strongly considered in patients with thyroid nodules 4 cm or larger regardless of FNAB cytologic test results.

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Author Contributions: Study concept and design: Pinchot and Chen. Acquisition of data: Pinchot, Al-Wagih, Schaefer, and Sippel. Analysis and interpretation of data: Pinchot and Sippel. Drafting of the manuscript: Pinchot and Al-Wagih. Critical revision of the manuscript for important intellectual content: Pinchot, Schaefer, Sippel, and Chen. Statistical analysis: Pinchot. Obtained funding: Chen. Administrative, technical, and material support: Schaefer and Chen. Study supervision: Sippel and Chen.

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Clive Grant, MD, Rochester, Minnesota: This paper by Pinchot et al reinforces other similar reports raising concern that FNAB is unacceptably inaccurate in discriminating benign from suspicious or malignant large thyroid nodules. It is only fair to disclose to the audience that our group is publishing a manuscript that has different findings from this manuscript. The authors are well aware of this. I have several questions.

1. Although the study initially included 155 patients, only 97 had preoperative FNAB. Since 23 were indeterminate and 11 were malignant, they were appropriately operated on. The 11 with nondiagnostic cytology should not be considered further since no meaningful information was gleaned from the FNAB. Therefore, the study narrows to 52 patients with benign cytology with a total of 4 false-negative diagnoses, 8%. One of the 4 false-negatives was a nodule containing a single focus of papillary thyroid carcinoma. Legitimately excluding this patient, the false-negative rate would be 6%. Can you tell us what your false-negative rate is for nodules less than 4 cm in size, and whether it is statistically different from 0% or even 8%?

2. You did not give us any criteria that the cytologist used to define the slides as adequate for interpretation and specifically criteria for the diagnosis of benign. What were those criteria?

3. From the manuscript, it appears that you the authors, rather than the cytologist, actually assigned the diagnosis of benign to many of these nodules, depending on the presence of keywords or phrases in the cytology report. These included the word “cyst,” which our cytologist would almost certainly categorize as unsatisfactory; and “no evidence of malignancy,” which is really a comment lacking any definitive diagnosis. In addition, you included the label “adenoma” as benign. Yet you describe later in the manuscript as “worrisome” the finding that...
some of these were follicular adenomas when surgically excised. There is a contradiction here and I would like you to clarify this.

4. Finally, you did not address the sources of error in your specific false-negative results. We would consider 3 possibilities:
   - Sampling error. It seems that actually missing a 4-cm or larger nodule with a needle would be very unlikely.
   - With very rare exception, a cancerous nodule is malignant throughout the entire nodule. So a needle aspirate anywhere from within the nodule should yield either malignant or suspicious cytology. Perhaps your patient with the single focus of papillary microcarcinoma is one of these rare exceptions.
   - Cytology interpretation error. This seems most likely.

Have you determined the errors for your patients? If cytology interpretation was the source, why would samples from larger nodules be any more likely to be incorrect than samples from small nodules, which is the central point of this study?

Dr Chen: I am just going to start with an overall comment. The problem with studies that have been published like our current one is that they often involve a very heterogeneous population with different operative indications. We are not necessarily resecting all thyroid nodules greater than 4 cm. In fact, during the study period, we had 4 different surgeons, and only 1 of those surgeons routinely took all large thyroid nodules. Therefore, we do not know the true number of patients who have nodules greater than 4 cm that have malignancy. When I started at the University of Wisconsin, our practice did not routinely take out large nodules with benign FNABs. In fact, the endocrinologists would refer these patients for surgery and I would say no. However, when the paper from Pittsburgh was published stating the high rate of neoplastic and malignant disease in large thyroid nodules, I was worried that I was potentially doing the wrong thing. Thus, we wanted to review what the accuracy of our FNAB results were for nodules greater than 4 cm.

Now, to get to your questions. Your first question asked about what is our false-negative rate for nodules less than 4 cm, and we do not know this number definitively. However, we have published previous series where we have examined our accuracy of FNAB overall. For all patients, the false-negative rate is about 4% to 6%. Therefore, if we can extrapolate these data to the subgroup of patients with thyroid nodules less than 4 cm, I would estimate that the false-negative rate is 4%. Whether or not this is statistically different from the 8% rate in patients with nodules greater than 4 cm is not clear.

Your second question was regarding the FNAB criteria for adequacy at our institution. In the literature, this is very controversial, but at our institution we will call an FNAB adequate if we see 6 or more groups of 10 follicular cells in 2 separate aspirates.

Your third question focused on the assignment of the diagnosis. The assignments for the diagnosis on the FNABs were actually the reports from the cytologists. The words that you read in the manuscript are actually the words the cytopathologist used.

Lastly and, perhaps more importantly, you asked what are the sources of error for FNAB in large thyroid lesions. We are in the process of reviewing this on a case by case basis with our cytopathologists. I would estimate that it is a combination of all the things you listed: sampling error, having part of the nodule that is malignant, and the interpretation. There is probably a fourth factor as well. We are assuming that the final pathologic diagnosis is definitive and not affected at all by the size of the lesion. It could be that when we take out larger nodules the pathologist is more likely to call them neoplastic. Another limitation of this study, as well as others, is that we only have definitive pathology on the patients who undergo surgery.

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