Diagnostic Criteria and Risk-Adapted Approach to Indeterminate Thyroid Cytodiagnosis

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Significant numbers of overdiagnoses of thyroid needle biopsies as “indeterminate” create a risk of surgery for benign disease. Overdiagnoses can be reduced by appropriate criteria and a risk-adapted approach to cytodiagnosis. Cancer (Cancer Cytopathol) 2010;118:415–22. © 2010 American Cancer Society

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The rate of diagnosis of well-differentiated thyroid cancer in the United States is increasing more than that of any other solid tissue malignancy1 with an estimated 44,670 new diagnoses in 2010.2 Following identification of thyroid nodules, diagnosis is based on ultrasound and biopsy studies. Increased availability and affordability of ultrasound machines, coupled with a large increase in incidental nodules detected at other imaging studies, has resulted in a large increase in the number of nodules being evaluated. An estimated 432,000 patients undergo analysis of thyroid nodules annually.3

Approximately 15% of thyroid biopsies demonstrate indeterminate cytology3 of which microfollicular neoplasm is the most common at Outpatient Pathology Associates, a 4-person private practice group in Sacramento operating a fine-needle biopsy clinic and providing diagnostic services to physicians in more than 20 states. Because most guidelines recommend this diagnosis as an indication for surgery,4-6 it may lead to more than 50,000 operations annually. As most cases identified as indeterminate are in reality benign, this may represent up to 35,000 unnecessary operations. One estimate projects the cost of care for such nodules at more than $1 billion over the next 2 years.3

At Outpatient Pathology Associates during the last 25 years, the rate of all indeterminate diagnosis of 51,000 adequate biopsies has been 5% with no legal allegation of failure to diagnose thyroid cancer. We suggest that the national rate of 15% results, in large part, from overdiagnosis. Problems include poor slide preparation, pseudocomplexity due to artifact, failure to distinguish between macrofollicular and microfollicular patterns, and failure to recognize benign microfolicles as in chronic thyroiditis. Overdiagnosis can be further reduced by using a risk-adapted approach to diagnosis similar to Tuttle’s recommendation for treatment of thyroid cancer.7
The American Cancer Society’s (ACS) 2010 annual statistics publication groups the estimated new cancer diagnoses and new cancer deaths into 13 organ systems. To compare risks of cancer death, we calculated the 2010 estimated new case to death ratio, \( C_n/D \). For a very lethal cancer, this approaches 1. A type of cancer which kills only a small percentage of patients has a much greater \( C_n/D \). Table 1 is adapted from the ACS 2010 annual statistics. The \( C_n/Ds \) ranged from 1.5-2 for the more deadly gastrointestinal and respiratory cancers to 5 for breast and genital cancer. Thyroid carcinoma is 5-7 times less common than any of the preceding; its \( C_n/D \) is 26.4, and there are only about 1700 annual deaths in the United States.

Therefore, the aim of thyroid cancer diagnosis is less the reduction of mortality and more the prevention of morbidity from local recurrence and metastases. Because prompt diagnosis and surgery may be lifesaving for breast cancer victims, noninterventional observation of microcalcifications is not performed. In contrast, regular sonographic surveillance may offer a better risk to benefit ratio than surgery for many low risk indeterminate thyroid nodule cases.

The first source of diagnostic error is nomenclature. Of the terms “follicular lesion of undetermined significance”, “follicular neoplasm”, and “microfollicular neoplasm”, the most accurate is the latter because the risk of follicular carcinoma resides specifically in the microfollicular architecture. This point is evident even in early articles, such as that of Hazzard. Although his article focused on what constitutes true vascular invasion, the photomicrographs show a pure microfollicular pattern. In their classic fascicle on thyroid tumors, Rosai and colleagues emphasized the significance of microfollicular architecture in follicular carcinoma by noting that few follicular carcinomas exhibit normofollicular or macrofollicular patterns. They recommend raising diagnostic suspicion whenever encountering a follicular neoplasm with a predominantly solid, trabecular, or microfollicular pattern. More recently, Chan made a similar statement that the presence of solid, trabecular or microfollicular growth patterns should heighten the suspicion for follicular carcinoma leading to a diligent search for vascular or capsular invasion. The illustrations that Rosai and Chan provide are examples almost exclusively of solid, trabecular, or microfollicular growth patterns. None show any significant macrofollicular content. At a practical level, there is no such thing as vascular or capsular invasive predominantly macrofollicular follicular carcinoma (as distinct from the rare macrofollicular papillary thyroid carcinoma).

Thus, follicular neoplasm, by not emphasizing this critical microarchitectural feature, has allowed hypercellularity alone to be used mistakenly as a criterion for true microfollicular neoplasm. We regularly see consultation cases in which hypercellular smears of macrofollicles or orderly monolayer sheets (the fragments of macrofollicles) have been wrongly interpreted as “follicular neoplasm” with a recommendation for surgery. Hypercellularity alone is not an independent criterion of malignancy. Accordingly, we would argue that “follicular neoplasm” and “follicular lesion” should be replaced by “microfollicular neoplasm” and “microfollicular lesion” for diagnostic clarity and to protect against this all too common diagnostic error.

The second diagnostic pitfall is that of pseudocomplexity. This may result from mechanical smear distortion, clot artifact (Fig. 1), or bloody dilution with secondary roll artifact, and, thus, this pseudocomplexity can produce appearances that may create a diagnosis of microfollicular neoplasm when the artifact is not recognized. The extreme distortion that clot artifact can impose on cells is clearly demonstrated in Figure 2.

Poor biopsy or smearing technique remain the primary but correctable cause of pseudocomplexity. For example, clot artifact can be reduced by limiting needle dwell time in a nodule to 3-5 seconds (as recommended by the National Cancer Institute’s Thyroid Fine-Needle Aspiration State of the Science Conference) and by using ultrasound guidance to sample multiple fresh areas within nodules. An excellent reference for fine-needle

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**Table 1. New Cancer Cases and Deaths, 2010**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>New Cases No. (%)</th>
<th>New Deaths No. (%)</th>
<th>Cases/Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites</td>
<td>1,529,560</td>
<td>569,490</td>
<td>2.7</td>
</tr>
<tr>
<td>Genital</td>
<td>311,210 (20)</td>
<td>60,420</td>
<td>5.2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>274,330 (18)</td>
<td>139,580</td>
<td>2.0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>240,610 (16)</td>
<td>161,670</td>
<td>1.5</td>
</tr>
<tr>
<td>Breast</td>
<td>209,060 (14)</td>
<td>40,230</td>
<td>5.2</td>
</tr>
<tr>
<td>Thyroid</td>
<td>44,670 (2.9)</td>
<td>1,690 (0.3)</td>
<td>26.4</td>
</tr>
<tr>
<td>Female/Male</td>
<td>33,930/10,740 (3.1)</td>
<td>960/730 (1.3)</td>
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*Percentage of all sites.*
Figure 1. Pseudocomplexity secondary to clot artifact. The complexity of the group on the left results from fibrin clot. Threads of fibrin clot can be seen as fine linear light blue stands (arrows). A small remnant of a monolayer sheet not involved in this process is present just up and to the right of the solid black arrow. This complexity can be misinterpreted as the complex growth pattern of a microfollicular neoplasm if it is not recognized as an artifact.

Figure 2. Pseudocomplexity and marked cellular distortion by fibrin clot. The lower right half shows a broad zone of fibrin clot artifact in which a follicular sheet has been transformed into a complex appearing group. A nice example of the distorting power of fibrin clot can be seen in the adjacent red blood cells. The cells outside of the fibrin clot in the upper left half are well-formed circles whereas those with in the fibrin clot are distorted almost beyond recognition.
biopsy and smear preparation is Dr. Britt-Marie Ljung’s video, available at the Papanicolaou Society website. Supervised preparation of 100 slides is generally adequate to attain proficiency.

When pseudocomplexity is suspected, the diagnosis of microfollicular neoplasm should not be used, but rather a declarative statement such as, “Follicular cells present in a nondiagnostic pattern due to clot artifact; see note”. A well-written note can help refine the practitioner’s fine-needle biopsy technique by providing literature references and specific suggestions as previously noted.

The third common diagnostic error is misinterpretation of the microfollicular component of chronic lymphocytic thyroiditis. Histologically, a significant lymphocytic component is rarely seen within the capsule of a microfollicular nodule. Lymphoid hyperplasia, in most cases, provides a benign explanation for microfollicular content as chronic thyroiditis. This presumes that one has considered the possibility of papillary carcinoma infiltrating chronic thyroiditis. Fortunately, papillary thyroid carcinoma in chronic thyroiditis typically exhibits many overt features of papillary carcinoma. One need only consider papillary carcinoma in the differential diagnosis to make a correct diagnosis.

Similarly, we have seen consultation cases at Outpatient Pathology Associates where follicles of small diameter associated with what we refer to as benign follicular atrophy have been misinterpreted as microfollicular neoplasm. There are 2 distinctive features that characterize benign follicular atrophy. First, the nuclei are quite small, often smaller than red blood cells. Second, the cytoplasm is quite thin and delicate, often appearing weible or filamentous. These features are illustrated in Figure 3.

Misinterpreting benign follicular atrophy can result in erroneous diagnosis in 2 ways. First, these cells are so small that they may be completely overlooked when one is looking for the customary well-formed intact sheet, such as in Figure 3, particularly when there is increased blood in the background. Second, because of the atrophic character of the cytoplasm, the sheets, when smeared, tend to form small rounded groups that appear like microfollicles but differ with their distinctive atrophic
nuclear and cytoplasmic features (Fig. 4). Although it is true that some areas of degeneration in a true microfollicular neoplasm can have these features, when the overall sample has these features, it is benign. Microfollicles of microfollicular neoplasia usually have a nuclei size that is a little larger than red blood cells and an intact central core of well-preserved cytoplasm (Fig. 5). Less often, small atrophic follicles can have sharply demarcated perimeter cytoplasmic borders and are even more at risk of misinterpretation as microfollicles. However, these atrophic follicles have a very well-defined perimeter cytoplasmic border (Fig. 6) unlike true neoplastic microfollicles (Fig. 5).

Table 2 summarizes the conditions that are likely to produce the overdiagnosis of microfollicular neoplasm.

During the last 3 decades, the pathologist’s role in the diagnosis of thyroid disease has expanded from pure microscopic specimen evaluation to include pathologist-performed needle aspiration biopsy and ultrasound-guided fine-needle biopsy, as we have done at Outpatient Pathology Associates. The logical outcome has been the evolution of the clinical cytologist, as the pathologist integrates more immediate clinical and patient information to use in arriving at a diagnosis and recommended follow-up. Although this is not presently a common practice in most pathology groups, that is changing as the College of American Pathologists began a Ultrasound-Guided Fine-needle Aspiration Certificate Program in June 2009 similar to the Endocrine Certification Neck Ultrasound program offered by the American Association of Clinical Endocrinologists.

In situations such as breast cancer evaluation, the goal is to maximize diagnostic speed and certainty so that treatment can begin without delay. For differentiated thyroid cancer with its slow growth rate and limited lethality, a pathologist may reasonably take a risk-adapted approach using the patient’s history, ultrasound findings, and cytology results to suggest ultrasound monitoring at 6-18-month intervals instead of surgery.

Ultrasonographic features that make a nodule more suspicious for malignancy include: a significant increase in size (20% increase in nodule diameter with a minimum...
Figure 5. Microfollicles in microfollicular neoplasm. The true microfollicles associated with microfollicular neoplasia have nuclei larger than red blood cells, nuclear overlap, and a well-preserved central cytoplasmic core. The cytoplasm usually does not extend beyond the perimeter of the follicle.

Figure 6. Well-formed small diameter follicles in benign follicular atrophy. Less commonly in benign follicular atrophy one can see extremely well-formed small diameter follicles. These characteristically have well-margined perimeter cytoplasm unlike the absence of this in neoplastic microfollicles (Fig. 5). Additionally, these occur in association with usual features of atrophy as illustrated in Figure 3.
at 2 or more dimensions of at least 2 mm),
5 hypoechoic echotexture, irregular or infiltrative margins, intranodular vascularity,
16 microcalcifications, coarse calcifications, interrupted rim calcifications, abnormal lymph nodes, and anterior-posterior dimension greater than transverse dimension.
5,6,17,18 Clinical features that make a thyroid cancer more likely to behave aggressively include: age older than 60 years or younger than 20 years, size greater than 4 cm, rapid growth, extrathyroidal extension, and abnormal lymph nodes.
5-7

Here are 2 case illustrations. Case 1: A patient has a new thyroid nodule. The biopsy produces good quality smears showing a 60% microfollicular cell population and the rest monolayered sheets. There is no lymphocytic background or stainable colloid. All groups are devoid of nuclear cytologic features of follicular variant of papillary carcinoma. The cytologic diagnosis would likely be microfollicular neoplasm. In the risk-adapted approach to diagnosis, the additional data that the cytologist might consider is that the patient is a 28-year-old female with a 12 mm nodule having only the low risk ultrasound features of homogenous hypoechogeticity, a uniform thin halo, no intranodular blood flow on power Doppler analysis, and no calcifications. Here, the quantifiable risk of surgery may be greater than the risk of ongoing surveillance.

Case 2: The next patient’s biopsy sample has smears of good quality showing 30% microfollicular content with the remaining 70% monolayered sheets absent papillary features. The pure cytologic diagnosis might be benign thyroid nodule or follicular lesion of undetermined significance. The risk-adapted approach would consider that this is a 65-year-old male whose nodule has grown from 3.8 to 4.5 cm during 6 months and has fractured eggshell calcification with strong intranodular blood flow. Here, a reasonable risk-adapted diagnosis is microfollicular neoplasm and a recommendation for surgery.

In surgical pathology, a false-negative rate of less than 1% for a breast biopsy specimen is appropriate and obtainable. However, when interpreting thyroid needle biopsy, we accept false negative rates of 1% to 3% for benign nodules and 5% to 10% for follicular lesions of undetermined significance as a known test parameter that is monitored by surveillance ultrasound and repeat needle biopsy as indicated. The slow growth and low mortality of differentiated thyroid carcinoma makes this risk-adapted approach a better alternative than surgery in these selected cases. As Tuttle7 has so clearly summarized, “risk stratification is an active, ongoing process in which risks are adjusted on the basis of accumulated clinical data, rather than considered as a static initial assessment that does not change”. The interpretation of cytological findings is part of an ongoing Bayesian process in which a patient’s risk of thyroid cancer begins with an assessment of clinical risk, is modified by the ultrasonographic appearance, and is ultimately determined by the results of the cytology. Improvement in diagnostic accuracy results from consideration of all of these factors together, rather than any individual result in isolation.

A review of our Outpatient Surgical Pathology data for thyroid fine-needle biopsy shows a 25-year indeterminate rate of 5%. From 1984 to 2009, we had only 2734 indeterminate diagnoses in 51,653 cases. From 2005 to 2009, our overall indeterminate rate actually decreased to 4.1% including a 1.9% microfollicular neoplasm rate and a 1.6% suspicious papillary thyroid carcinoma rate (705, 321, and 271 of 17,033 cases, respectively). This low indeterminate rate reflects 3 factors. First, we are careful to avoid overdiagnosis as described in this commentary and summarized in Table 2. Second, we work diligently with our referring physicians to help them optimize biopsy acquisition. Last, we use a risk-adapted approach when we perform our own ultrasound-guided fine-needle biopsies and request clinical information from our referring physicians.

We provide a diagnosis including the risk of cancer on the basis of the microscopic findings, ultrasound, and clinical features. We also suggest a follow-up plan based on the risk assessment individualized for each patient. Considering all of the above factors, surveillance may be a reasonable, safe, and cost-effective alternative to surgery for many patients with this subset of thyroid nodules.

Table 2. Factors Reducing Excess Indeterminate Diagnoses

<table>
<thead>
<tr>
<th>Factors</th>
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<tbody>
<tr>
<td>1 Hypercellularity due to perfect monolayered sheets does not imply microfollicular neoplasm.</td>
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<tr>
<td>2 Artifact pseudocomplexity does not imply microfollicular neoplasm.</td>
</tr>
<tr>
<td>3 Proper biopsy and smearing techniques minimize artifact pseudocomplexity.</td>
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<tr>
<td>4 Atrophic follicles of small diameter do not imply microfollicular neoplasm.</td>
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<tr>
<td>5 Nonpapillary microfollicles in chronic thyroiditis do not imply microfollicular neoplasm.</td>
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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES