

# Post-thyroid FNA Testing and Treatment Options: A Synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference

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*The National Cancer Institute (NCI) sponsored the NCI Thyroid Fine Needle Aspiration (FNA) State of the Science Conference on October 22–23, 2007 in Bethesda, MD. The 2-day meeting was accompanied by a permanent informational Web site and several on-line discussion periods between May 1 and December 15, 2007 (<http://thyroidfna.cancer.gov>). This document addresses follow-up procedures and therapeutic options for suggested diagnostic categories. Follow-up options for “nondiagnostic” and “benign” thyroid aspirates are given. The value of ultrasound examination in the follow-up of “nondiagnostic” and “benign” thyroid aspirates is discussed. Ultrasound findings requiring reaspiration or surgical resection are described as are the timing and length of clinical and ultrasonographic surveillance for cytologically “benign” nodules. Options for surgical intervention are given for the diagnostic categories of “atypical/borderline,” “follicular neoplasm,” “suspicious for malignancy” and “malignant” (<http://thyroidfna.cancer.gov/pages/info/agenda/>). *Diagn. Cytopathol.* 2008;36:442–448. © 2008 Wiley-Liss, Inc.<sup>†</sup>*

**Key Words:** thyroid; fine-needle aspiration; follow-up; ultrasound; nondiagnostic; indeterminate; follicular neoplasm; papillary carcinoma

The authors of this document are members of Committee VI. The charge of this committee was to evaluate possible post-FNA testing and treatment options. This area was further subdivided into discussion topics, designated A–F in the discussion that follows (<http://thyroidfna.cancer.gov/pages/info/agenda/>). This is a summary of the “Review and Conclusions” of the subject matter that this committee analyzed based on several parameters: literature reviews limited to English language publications dating back to 1995 using PubMed as the search engine with key words determined by the committee members; online forum discussions (<http://thyroidfna.cancer.gov/forums/default.aspx>), and formal interdisciplinary discussions

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The following medical societies are co-sponsors of the NCI Thyroid Fine Needle Aspiration State of the Science Conference and Website: The American Cancer Society, College of American Pathologists, The American Society for Clinical Pathology, The American Society of Clinical Oncology, La Societe Francaise de Cytologie Clinique, The American Society of Cytopathology, The Papanicolaou Society of Cytopathology, The American Association of Clinical Endocrinologists, The American Association of Endocrine Surgeons, The American Thyroid Association, The Society of Radiologists in Ultrasound, The American College of Radiology, National Comprehensive Cancer Network, The American College of Endocrinology.

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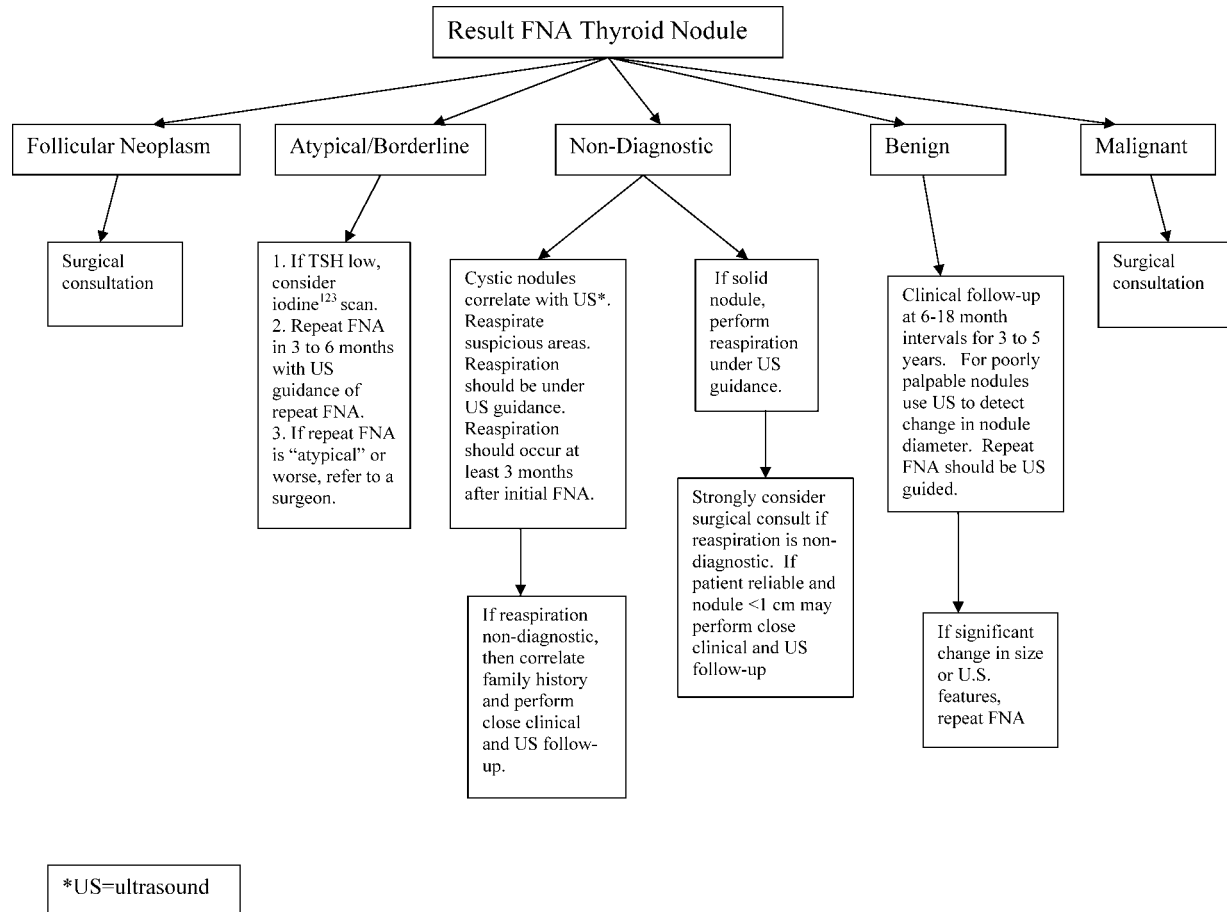


Fig. 1. A potential post-FNA protocol for follow-up and treatment of a thyroid nodule.

held at the October 2007 conference. This is not a “standards of practice” guideline, nor is it endorsed as such by the National Cancer Institute.

The success of fine-needle aspiration (FNA) in the evaluation of thyroid nodules depends on the utilization of reproducible diagnostic categories associated with widely accepted follow-up and therapeutic strategies. Diagnostic categories should result in similar follow-up and management strategies among institutions and physicians managing and treating patients with thyroid nodules. This document addresses management strategies associated with the diagnostic categories designated as “nondiagnostic,” “benign,” “atypical/borderline,” “follicular neoplasm,” “suspicious for malignancy,” and “malignant.” These categories are further discussed in the accompanying article by Baloch et al.<sup>1</sup> Figure 1 shows a potential approach to management of thyroid nodules.

#### Follow-Up of “Nondiagnostic” FNA Results

A universally accepted approach to “nondiagnostic” thyroid fine-needle aspirates (FNAs) remains lacking, but the

American Thyroid Association (ATA) has proposed a set of strategies that are currently widely accepted.<sup>2</sup> The following strategy for post-FNA testing and treatment is based partially on the ATA recommendations as well as the guidelines developed by The American Association of Clinical Endocrinologists with The American Association of Endocrine Surgeons,<sup>3</sup> The British Thyroid Association in conjunction with The Royal College of Physicians<sup>4</sup> and The Comprehensive Cancer Network<sup>5</sup> along with proposals discussed at the NCI State of the Science Conference in October of 2007.

Nondiagnostic aspirates may be due to the qualitative or quantitative nature of the material received. Clearly, aspirates distorted by abundant blood or otherwise technically compromised because of smearing, fixation, or staining artifacts are nondiagnostic. The quantitative aspect of specimen adequacy is more controversial. It is clear that smear cellularity depends on several factors including the aspirator’s skill and the intrinsic nature of the thyroid nodule.<sup>6</sup> The cellularity is most germane for adequacy assessment of cystic and partially cystic thyroid nodules. All thyroid cysts should be completely drained and the

cyst wall should be sampled. Specimens obtained from cystic nodules may yield two types of specimens. One in which the material is composed of pure colloid without an epithelial component. The second type is watery fluid in which are dispersed a number of histiocytes and histiocyte-like cells with varying degrees of nuclear atypia. Aspirates composed of pure colloid and lacking a cellular component can be considered benign rather than “nondiagnostic.” Aspirates of cysts containing blood and histiocytes, but no epithelial cells need correlation with ultrasound findings.<sup>7</sup> If ultrasound examination discloses suspicious areas, these aspirates should be considered “nondiagnostic.” Cystic lesions yielding “nondiagnostic” aspirates should undergo repeat FNA either with or without ultrasound guidance. (For a further discussion of the indications for repeat FNA, please see the accompanying article in this issue by Cibas et al.)<sup>8</sup> When repeat FNA yields a “nondiagnostic” aspirate, close clinical follow-up or surgery has been recommended by the ATA. Solitary nodules that are repeatedly “nondiagnostic” on fine-needle aspiration have an unknown risk of malignancy, but it is probably between 5 and 10%.<sup>9</sup> The choice of clinical or surgical follow-up in nodules with repetitively “nondiagnostic” results is left to the discretion of the clinician. Many cystic nodules contain only central colloid surrounded by a thin rim of follicular epithelium, and even when drained and the cyst wall sampled, little or no follicular epithelium is obtained. These cysts are at very low risk for harboring malignancy and their precise follow-up has been controversial.

Surgical resection of these nodules will result in a high percentage of nonneoplastic specimens which do not require surgery for therapeutic reasons. Hence, many authors have recommended that management of these cysts in reliable patients is best achieved by clinical/non-surgical follow-up. Other authors point to the low, but real incidence of cystic papillary carcinoma in these cystic nodules. Based on this low incidence of carcinoma, they recommend surgical resection of the nodule following two “nondiagnostic” aspirations. Timing of repeat FNA has not been established, but 6–18 months appears to be a reasonable interval.

The ATA recommends that solid nodules associated with a “nondiagnostic” smear should be reaspirated with ultrasound guidance, and if repeat aspirates remain “nondiagnostic,” surgery should be strongly considered.<sup>2</sup> Repeat aspirates should be performed with the assistance of cytopathology whenever possible.<sup>10</sup> Some authors recommend that solid nodules less than 1 cm in size and associated with a “nondiagnostic” repeat aspirate should be followed by ultrasound and only undergo surgical resection if enlargement is documented on repeat ultrasound examination.<sup>7</sup> For further discussion of this topic, please see the accompanying article in this issue by Cibas et al.<sup>8</sup>

## Conclusions

1. Cystic lesions with an initial “nondiagnostic” aspirate should undergo a repeat FNA if ultrasound examination demonstrates suspicious areas. The repeat FNA should be under ultrasound guidance, and when possible, intraprocedural review of the aspirated material by a cytopathologist is optimal. The cyst should be completely drained and the cyst wall sampled. When repeat FNA yields “nondiagnostic” material, correlation with family history and close clinical and ultrasonographic follow-up should be performed. Repeat FNA can be performed in 6–18 months at the discretion of the clinician.
2. Solid nodules associated with “nondiagnostic” aspirates should be reaspirated with ultrasound guidance and whenever possible intraprocedural review by a cytopathologist. If repeat smears are “nondiagnostic,” surgery should be strongly considered. If the patient is considered reliable and likely to return for clinical follow-up and the nodule is 1 cm or less in size, close clinical follow-up with ultrasound examination is a reasonable alternative to surgery. When growth of the nodule is detected during ultrasound surveillance, excision is appropriate.
3. In general, a waiting period of at least 3 months should elapse between the initial “nondiagnostic” aspirate and reaspiration. If suspicion for a carcinoma is high based on clinical or ultrasonographic features, a shorter waiting period may be appropriate in some patients.

## Follow-Up of “Benign” FNA Results

Fine-needle aspirates yielding a diagnosis of “benign” include the categories: nodular goiter, multinodular goiter, colloid goiter, and Hashimoto’s thyroiditis. The precise management of these benign and nonneoplastic entities has varied over time and between institutions. Because patients with multiple thyroid nodules have the same risk of malignancy as those with only a single nodule, follow-up of patients with multiple nodules should be the same as those with a solitary dominant thyroid nodule. Cytologically “benign” thyroid nodules require careful clinical follow-up because up to 5% false-negative rate is associated with a “benign” cytologic diagnosis.<sup>11,12</sup> The false-negative rate may be higher with FNAs directed by palpation rather than by ultrasound examination.<sup>13,14</sup> Thus, cytologic diagnoses obtained by palpation directed FNAs may require closer clinical follow-up than those diagnoses obtained by ultrasound-guided FNAs. Certain ultrasonographic characteristics indicate a higher likelihood of malignancy and include microcalcifications, hypoechogenicity in a solid nodule, and intranodular hypervascularity.<sup>15,16</sup> These nodules may require more frequent clinical

and ultrasonographic follow-up after a “benign” diagnosis is rendered by fine-needle aspiration.

Options for follow-up of “benign” nodules by FNA have included reaspiration,<sup>17</sup> hormone suppressive therapy, and clinical follow-up with repeat ultrasound examinations. Routine medical suppressive therapy to confirm a “benign” cytologic diagnosis remains controversial. Multiple randomized trials have shown that thyroid hormone suppression may result in a decrease in nodule size for patients with borderline low iodine intake. The data are less convincing in populations ingesting sufficient iodine.<sup>18–20</sup> Also, rare examples of thyroid hormone suppression of papillary and follicular carcinomas have been reported. From these data, it is unclear that thyroid hormone suppressive therapy is a reliable test for confirmation of a “benign” cytologic diagnosis of a solitary or dominant thyroid nodule.

Cytologically “benign” nodules can be followed clinically with repeat ultrasound examination at 6 to 18 month intervals. These nodules may be reaspirated or surgically removed when significant change in size occurs. Ultrasonography appears to be the best technique for detection of change in nodule size.<sup>21</sup> Unfortunately, there is no general agreement as to what a significant change in size of a nodule is that necessitates reaspiration or surgical resection. The ATA has suggested that a 20% increase in nodule diameter with a minimum increase in two or more dimensions of at least 2 mm is a reasonable definition for a significant change in nodule size.<sup>1</sup> The American Thyroid Association has recommended clinical follow-up of cytologically “benign” and easily palpable nodules to occur at 6–18-month intervals. When nodules are not readily palpable, the recommendation is for serial ultrasound examination at 6–18-month intervals following the initial “benign” cytologic diagnosis.<sup>2</sup> When there is evidence for nodular growth either by palpation or ultrasonography, repeat FNA should be performed preferably under ultrasound guidance.<sup>2</sup>

### Conclusions

1. Thyroid nodules cytologically diagnosed as “benign” require careful clinical follow-up. Easily palpable thyroid nodules may be followed clinically at 6–18-month intervals. Nodules that are not readily palpable should receive serial ultrasound examinations at 6–18-month intervals. The duration of the follow-up period is not fully defined, but should be at least 3–5 years following the initial “benign” cytologic diagnosis.
2. If a 20% increase in nodule diameter or a minimum of a 2-mm increase in two dimensions is detected either by palpation or ultrasonography, repeat fine-needle aspiration is appropriate. Repeat FNA should also be performed if ultrasound abnormalities (irreg-

ular margins, central hypervascularization) develop. The repeat fine-needle aspiration should be performed under ultrasound guidance. The attendance of a cytopathologist at the reaspiration procedure is optimal to assess sample adequacy.

3. At this time, hormone suppressive therapy cannot be recommended as a diagnostic maneuver for confirmation of benignancy in a cytologically “benign” thyroid nodule.
4. Ethanol ablation may be considered in selected patients.

### Follow-Up of “Atypical/Borderline” FNA Results

A variety of terms are employed by laboratories to convey uncertainty about the significance of thyroid cytologic findings. Such changes do not rise to the level of a significant concern for a follicular neoplasm meriting lobectomy (see below), nor do they fit a “suspicious for malignancy” interpretation (see later). Because of some (usually focal and/or mild) cytologic or architectural atypia, neither can such cases be reliably called benign. A variety of diagnostic headings are used to report such cases. These include “atypical follicular lesion,” “cellular follicular lesion,” and “indeterminate.” (The term “indeterminate” has also been used by some laboratories to mean “follicular neoplasm” as discussed in the next section.) The term “atypical/borderline” will be used for the remainder of this discussion. For additional discussion, see the accompanying article in this issue by Baloch et al.<sup>1</sup>

The lack of agreement on terminology for this category has led to variability in the percentage of these lesions which are malignant. In a majority of series, ~5–10% of the “atypical/borderline” category are malignant neoplasms with the remaining 90–95% being adenomas or dominant nodules of a multinodular goiter.<sup>22,23</sup> Other authors have reported a 20–30% malignancy rate.<sup>24–26</sup> Given that this diagnostic category is associated with low specificity and a low positive predictive value, the appropriate follow-up or therapy for the category remains controversial. Some authorities have recommended repeat FNAs, repeat ultrasound scans, or radionuclide uptake studies. A repeat FNA is benign in about one-half of patients, obviating the need for surgery.<sup>27</sup> Some reports have even suggested the use of liquid-based cytology and immunocytochemistry to improve diagnostic accuracy.<sup>28–34</sup>

Radiological correlation may also be helpful in improving the overall positive predictive value of the “atypical/borderline” category. Besides increasing size, ultrasonographic features such as hypoechogenicity, irregular nodular border, calcifications, and abnormalities of vascularization all favor a malignant diagnosis.<sup>35,36</sup>

Although no consensus has been reached concerning the value of iodine-123 scans, it may be useful in selected cases. In cases cytologically designated as “atypical/bor-

derline,” and when the serum TSH level is low or below normal the referring clinician may consider an iodine-123 scan. If the scan is “hot,” clinical follow-up with a repeat FNA in 3–6 months is appropriate. If the scan is “cold,” the patient may be referred for surgery. In patients who are suboptimal operative candidates, close clinical follow-up with repeat ultrasound to detect an increase in nodule size, abnormalities of vascularization or the presence of calcification can be performed to increase the diagnostic accuracy of the “atypical/borderline” category.

The utility of outside “expert” consultation is debatable, but in some patients where reaspiration is not easily attainable, expert consultation may be a reasonable alternative to reaspiration or surgery.

### Conclusions

1. Outside expert cytopathology consultation may be considered in cases with an “atypical/borderline” cytologic diagnosis.
2. In general, a conservative approach is recommended. After a single “atypical/borderline” interpretation, a repeat FNA should be considered in 3–6 months. If the repeat FNA is “atypical/borderline” or worse, a surgical consultation should be considered.<sup>27</sup>

### Follow-Up of an FNA Diagnosis of “Follicular Neoplasm”

This category has in some reports been termed “Suspicious for Follicular Neoplasm.”<sup>24–27,35</sup> The category of “Neoplasm” generally refers to follicular neoplasms with the majority being adenomas. The category is associated with a 20–30% incidence of malignancy.<sup>2,22,24–26</sup> Because of the high incidence of malignancy associated with this diagnostic category, operative intervention has been recommended.<sup>2</sup>

### Conclusions

1. Patients with a diagnosis of “follicular neoplasm” or “suspicious for follicular neoplasm” should be referred to a surgeon for operative exploration. Usually, a lobectomy is performed followed by histologic examination of the lesion for capsular and/or vascular invasion. In some cases, total thyroidectomy may be performed. The choice between lobectomy and total thyroidectomy depends on a variety of factors including the presence or absence of nodules in the contralateral lobe and the characteristics of the index nodule combined with the age of the patient.
2. There is little support in the literature for frozen section evaluation to intraoperatively separate follicular adenomas from follicular carcinomas. If capsular or

vascular invasion is documented, total thyroidectomy may be performed. When capsular or vascular invasion is not identified, the operation may be completed by lobectomy.

3. When frozen section is not utilized, the initial surgery is usually limited to lobectomy. If subsequent histologic examination discloses capsular or vascular invasion, the diagnosis follicular carcinoma is made. Depending on the discretion of the surgeon, the histopathologic characteristics of the carcinoma and the clinical status of the patient, reoperation and total thyroidectomy may be performed.<sup>2</sup>

### Follow-Up of FNAs With a Diagnosis of “Suspicious for Malignancy”

In the majority of cases where this category is used, the cytopathologist is concerned that the nodule may represent a papillary carcinoma, but insufficient criteria are present for a definitive diagnosis.<sup>22</sup> Less commonly, other malignancies such as medullary carcinoma are included in this category. Approximately 50–75% of the lesions placed in this category are malignant.<sup>22,27</sup>

### Conclusions

Patients with an FNA diagnosis of “suspicious for malignancy” should be referred to a surgeon for consideration of thyroid lobectomy. Subsequent operative intervention depends on intraoperative or postoperative histologic review. Intraoperative frozen section may be of significant aid in determining the extent of surgery when a definitive diagnosis of papillary carcinoma is made by frozen section evaluation. Because of an increased risk of malignancy in this category, total thyroidectomy should be considered in patients with large tumors (>4 cm), when marked atypia is seen on FNA and in patients with a family or personal history of radiation exposure. Patients with bilateral nodular disease or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of future thyroid surgery on the contralateral lobe should be considered for total thyroidectomy.<sup>2</sup>

### Follow-Up of “Malignant” FNA Results

This category refers to the histopathologic entities of papillary carcinoma, medullary carcinoma, lymphoma, and anaplastic carcinoma. Little controversy exists that a positive cytologic diagnosis of malignancy in a thyroid nodule should be followed by a referral for surgery. In many cases, a definitive type of carcinoma can and should be cytologically diagnosed. Controversy exists as to the optimal surgical therapy for papillary carcinoma. The decision to perform lobectomy or total thyroidectomy is at the discretion of the surgeon and depends on a number of factors

including size and subtype of papillary carcinoma, patient age and patient health status. The ATA recommends total or near total thyroidectomy if any of the following features are present: primary carcinoma is more than 1–1.5 cm in size, contralateral thyroid nodules are present, regional or distant metastases are present, patient history of radiation to head or neck or a first degree relative with differentiated carcinoma of the thyroid. Patient age over 40 may also favor total thyroidectomy. However, if the cytology suggests metastatic cancer, a search to identify the primary site is required so that unnecessary thyroidectomy is avoided. The most common metastatic tumors are renal cell carcinoma, metastatic carcinoma of the lung and metastatic adenocarcinoma of the breast.

### Conclusions

1. The cytologic diagnosis of malignancy in the thyroid nodule should result in the referral of the patient for surgical consultation.
2. Whenever possible, the type of carcinoma present should be stated in the cytologic diagnosis.
3. It is mandatory that metastatic carcinoma be excluded whenever possible before surgical intervention is undertaken.
4. In certain clinical situations, surgical intervention may initially be simple lobectomy or lobectomy with intraoperative frozen section examination to determine if total thyroidectomy should be performed. When frozen section examination confirms the presence of a primary thyroid carcinoma, total thyroidectomy may be performed.<sup>2</sup> If frozen section is equivocal, the operative procedure is ended with a lobectomy, and further therapy is based on the findings of permanent sections.<sup>2</sup>
5. Depending on the patient's clinical status and the characteristics of the malignancy, total thyroidectomy may be performed for a cytologic diagnosis of papillary carcinoma.
6. Controversy exists as to whether total thyroidectomy or unilateral lobectomy should be performed in some cases of papillary carcinoma. The selection of lobectomy versus thyroidectomy depends on the evaluation of the patient's clinical status and the size and nature of the papillary carcinoma present. Papillary carcinomas under 1–1.5 cm in size and without unfavorable prognostic features may best be treated by simple lobectomy. Larger carcinomas and especially those over 4 cm in size should, in most cases, undergo total or near total thyroidectomy.
7. If total thyroidectomy is performed, it may be accompanied by a central compartment dissection. For patients with large bulky disease or recurrent la-

ryngeal nerve dysfunction, preoperative cross-sectional imaging should be considered as well as ultrasound imaging for lateral neck nodal disease.

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