AMERICAN THYROID ASSOCIATION

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Quality Assurance in Cytopathology and Histopathology of the Thyroid

ABOUT

This document is divided into a discussion of commonly encountered thyroid lesions and the optimal approach to sampling, specimen processing, and diagnostic reporting.

INTRODUCTION

This document will review the pathologic approach to specimens from thyroid lesions. Various types of specimens will be discussed; fine needle aspiration, core needle biopsy, and surgical specimens. The role of frozen section intraoperative evaluation is discussed, as well as challenging areas in thyroid pathology.

THYROID NODULE FINE-NEEDLE ASPIRATION

The increased use of sonography to examine the thyroid, as well as cross sectional imaging of the neck by computed tomography and magnetic resonance imaging, has resulted in the detection of many non-palpable thyroid nodules. A majority of all thyroid nodules are benign, but nodules, once discovered, require clinical and radiographic evaluation to determine whether a biopsy should be performed to exclude malignancy. Thus, fine-needle aspiration (FNA) has an essential role in the evaluation of patients with thyroid nodules. It reduces the rate of unnecessary thyroid surgery for patients with benign nodules and triages patients with thyroid cancer to appropriate surgery.

PUBLISHED GUIDELINES

There are a number of evidence-based published guidelines which address the selection of thyroid nodules for FNA, including those published by The American Thyroid Association (ATA), Society of Radiologists in Ultrasound (SRU), and American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association (AACE/AME/ETA). The core premise of each guideline is the knowledge that sonographic evaluation of thyroid nodular goiter has emerged as the primary imaging means to evaluate the malignant potential of thyroid nodules.

1. Technique of Fine-Needle Biopsy

   Prior to the widespread availability of thyroid ultrasound, most FNAs were performed by palpation. However, currently, in the United States and Europe, ultrasound guidance is used for the majority of thyroid nodule FNAs. Ultrasound guidance for FNA allows confirmation that a palpable abnormality truly corresponds to a discrete nodule, and allows selective targeting of specific nodules as well as targeting specific areas within a given nodule.

   a. The FNA specimen can be obtained by 25 or 27-gauge needle which can be either attached or not (non-aspiration technique or capillary action technique) to a syringe (usually 10 cc).

   b. The biopsy sample is obtained by gently moving the needle back and forth within the nodule.

   c. It is recommended to sample different portions of nodules. Most thyroid nodules, especially the benign ones, are heterogeneous in their architecture and cellular composition. Therefore, sampling one site within a thyroid nodule may not be truly reflective of the lesion and can lead to false negative or positive interpretations.

   d. A higher rate of cell adequacy has been reported with a thinner gauge needle. Ultrasound guidance also reduces the proportion of specimens yielding inadequate material for cytology analysis, especially for smaller nodules (measuring less than 1.5cm) and for partially cystic nodules. It has been shown that large numbers of passes (usually >4) in a thyroid nodule may not prove to be of value in acquiring a cellular sample, possibly due to increasing hemodilution.

2. Thyroid FNA specimen

   a. The FNA specimens should be immediately processed for cytomorphologic analysis. There are three main methods of sample preparation; smears, liquid-based preparations, and cell block--these preparation methods may be used singly or in combination. Smears are prepared on site, air-dried and alcohol fixed. Smears are prepared for staining with Romanowsky (Diff-Quik®, Wright-Geimsa) and Papanicolaou stains, respectively.

   Liquid based preparations include ThinPrep®, SurePath®, cytospin. Cell blocks are made with a variety of techniques to concentrate cellular materials which are then fixed in formalin and paraffin-embedded, much like a core biopsy or surgical specimen.

   b. Rapid onsite evaluation (ROSE) by a cytologist, when available, can be helpful in ensuring specimen adequacy and reducing number of passes. For some cases it may be possible on ROSE to perform a preliminary classification of the nodule, for instance differentiating between a primary and secondary thyroid lesion. ROSE also enables effective triage of the specimen for ancillary studies, if needed (flow cytometry, PTH, thyroglobulin and calcitonin measurement and molecular studies).

   c. The numbers of onsite smears should be kept to a minimum, preferably 2-3 smears per pass.

   d. The Romanowsky staining (Diff-Quik®) method is best for rapid onsite evaluation (ROSE) as it highlights the background colloid, follicular cells and other cellular elements. The Papanicolaou stain, performed on alcohol fixed smears is essential to study the nuclear details and cytoplasmic characteristics. These two staining modalities are complementary to one another.

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3. Fine-Needle Biopsy Cytology Results and Implications for Patient Care

In 2007, the National Cancer Institute sponsored the "Thyroid Fine Needle Aspiration State of the Science Conference" to develop criteria for consensus cytology classification, called the *Bethesda System for Reporting Thyroid Cytopathology (BSRTC)*. A key contribution of this system, in addition to defining criteria for specimen adequacy and characterizing benign and malignant lesions, was to define three specific categories within indeterminate samples, each correlating with a range of malignancy risk, resulting in a six tiered cytology classification. These indeterminate categories are necessary, as not all thyroid nodules will yield a sample that is definitively benign or malignant. The six *BSRTC* categories are:

1. Non-diagnostic
2. Benign
3. Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS)
4. Follicular or oncocytic (Hürthle cell) neoplasm or Suspicious for Follicular or oncocytic (Hürthle cell) neoplasm
5. Suspicious for malignancy
6. Malignant.

Recently, the second edition of *BSRTC* was published to refine the ranges for risk of malignancy for each diagnostic category (based on post *BSRTC 1st edition* published literature) and include new changes in the classification of follicular patterned lesions of thyroid.

4. BSRTC Diagnostic Categories

a. *Non-diagnostic:*

i. To be considered adequate for diagnosis, FNA samples must contain at least six groups of follicular epithelial cells, each comprised of 10-15 cells. These cells must be well-preserved and well-visualized.

ii. Exceptions to the cell adequacy criteria include: any samples with cytologic atypia, samples showing lymphocytic thyroiditis, or samples showing abundant colloid only.

iii. Factors which may contribute to a nondiagnostic FNA include: nodule composition, FNA technique and operator experience, and lack of on-site assessment of specimen adequacy.

iv. The non-diagnostic rate increased with the proportion of the nodule that is cystic and therefore ultrasound guidance is recommended for all FNA procedures when the nodule is partially cystic.

v. Repeat FNA with US guidance is recommended when a first FNA (performed without US) is non-diagnostic, and results in a diagnostic cytology specimen in 75% of predominantly solid nodules and 50% of cystic nodules.

It has been shown that approximately 5-7% of nodules will yield persistently non-diagnostic cytology results. For these nodules, the subsequent use of core-needle biopsy performed with a 20 or 21 gauge cutting needle under US guidance is of debatable utility, with some studies reporting success in procuring a diagnostic result and others failing to demonstrate this.

b. *Benign*

i. A benign cytology result occurs in approximately 60 to 70% of all thyroid FNAs.

ii. The overwhelming majority of nodules appropriately classified by the cytopathologist as benign turn out to be either a hyperplastic/adenomatoid nodule or a follicular adenoma.

iii. Other benign diagnoses include changes consistent with chronic lymphocytic thyroiditis or subacute thyroiditis. The false negative rate of a benign FNA cytology result for a malignancy is low (0 to 3%).

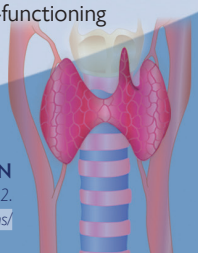
c. *Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS)*

i. This diagnosis represents a true gray zone in thyroid cytopathology, and occurs in about 3 to 6% of all FNAs.

ii. This diagnostic category includes cases that cannot be classified as either benign, suspicious, or malignant because of a wide variety of scenarios including poor specimen preparation or minimal atypical features in a minority of cells with an otherwise predominantly benign appearing sample.

iii. Atypia in thyroid FNA specimens can be nuclear atypia and/or architectural atypia. The former is usually seen as focal presence of either nuclear pleomorphism characterized by hyperchromasia and nuclear enlargement or presence of nuclear features suspicious but not enough to be classified as either suspicious or diagnostic for papillary carcinoma.

iv. Architectural atypia occurs when a portion of the specimen shows microfollicles or well-formed papillary architecture. It is prudent to understand that the majority of these nuclear and architectural atypical features are due to benign thyroid conditions such as degenerating hyperplastic/adenomatoid nodule, chronic lymphocytic thyroiditis and hyper-functioning adenomatoid nodules.



FURTHER INFORMATION

For more information on the survey findings, see *Thyroid, Vol. 27, No. 12.* https://www.thyroid.org/professionals/ata-publications/

v. It is recommended that nodules with this classification undergo repeat FNA and/or adjunct molecular testing for optimal clinical management.

d. *Follicular or oncocytic (Hürthle cell) neoplasm or Suspicious for Follicular or oncocytic (Hürthle cell) neoplasm*
   i. This cytology classification accounts for 6-12% of all FNA cytology results and carries a malignancy risk of 25-40%.
   ii. In the past this classification usually led to surgical excision since the distinction between a follicular cancer and a benign follicular adenoma requires surgical pathology assessment for vascular and/or capsular invasion.
   iii. Currently, many patients with nodules in this category undergo molecular testing of the sample to further stratify the risk of malignancy and possibly predict biologic behavior The additional information provided by molecular testing can ultimately influence choice of surgery (lobectomy vs. total thyroidectomy).

e. *Suspicious for malignancy*
   i. This category occurs in 3-5% of all FNA results.
   ii. The majority of these aspirates are diagnosed as suspicious for papillary thyroid cancer because some, but not all suspicious nuclear features of a papillary cancer are present or the changes are not widespread throughout the sample or the sample is sparsely cellular.
   iii. The risk of malignancy is 50-75% for all nodules in this category and surgery is recommended. For these patients, sonographic assessment of the central and lateral compartment cervical lymph nodes is recommended and if suspicious nodes are noted, an FNA of the node or nodes should be performed.
   iv. Adjunct molecular testing (TERT promoter mutation analysis) may also prove useful to assess the biologic behavior of malignancy.
   v. The malignant cases found on surgical follow-up includes cases of papillary thyroid carcinoma (both classic and follicular variant) and the recently described indolent neoplasm "non-invasive follicular tumor with papillary like nuclear features (NIFTP) formerly classified as encapsulated and non-invasive follicular variant of papillary thyroid carcinoma. Rarely for this category, other tumors such as medullary, anaplastic, and metastatic tumors are found on resection.

f. *Malignant*
   i. This diagnostic category is used when the cytomorphologic features are conclusive for malignancy.
   ii. The malignant tumors of thyroid diagnosed on FNA include papillary thyroid carcinoma and variant (mostly classic and tall cell variant), medullary thyroid carcinoma, poorly differentiated carcinoma, anaplastic carcinoma, metastatic carcinoma (history and with adjunct special studies such as immunohistochemistry) and lymphoma (combined with flow cytometry).
   iii. Most malignant tumors of thyroid origin are removed by thyroidectomy, but some lesions such as metastatic disease, lymphoma and anaplastic carcinoma may not necessarily be treated primarily with excision.

CORE NEEDLE BIOPSY:

Core needle biopsy results in between one and several cores of tissue which are fixed in formalin and processed as paraffin embedded fixed blocks. Slides are made for routine hematoxylin and eosin staining and, if needed, immunostaining or other ancillary studies can also be applied.

Core needle biopsies can be performed for two major categories of disease:

1. Diffuse disease to document lymphocytic thyroiditis.
2. Nodular disease to document the characteristic of a dominant or solitary thyroid nodule.

Expectation: The clinician submitting a core needle biopsy of the thyroid should expect the pathology report to:

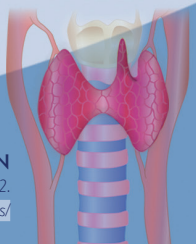
1. Document the type and severity of a diffuse disease such as lymphocytic thyroiditis; or to identify a neoplasm.
2. Characterization of neoplasms in core biopsies as to benign or malignant and its subtype if possible may be possible only in a minority of cases. Lesions that are classic papillary carcinomas should be diagnosed with ease. However, follicular lesions, which are far more common, rarely, if ever, can be definitively diagnosed on core biopsies.
3. In follicular patterned lesions and their oncocytic or Hürthle cell counterparts, the characteristic diagnostic criteria involve invasion of the capsule or of venous structures in the capsule. A core biopsy rarely can document such invasion. It is possible in many instances to identify a follicular patterned lesion as a neoplasm if it is monotonous and cellular.

THYROID SPECIMENS OBTAINED BY SURGERY

These types of specimens include lobectomy, lobectomy plus isthmusectomy, isthmusectomy alone, and total thyroidectomy. Some of these specimens will also be accompanied by sampling of regional lymph nodes. *(It is considered below the standard of care to excise a nodule in the thyroid lobe or isthmus; the initial approach should be a total isthmusectomy or more commonly a total lobectomy).*

FROZEN SECTION CONTROVERSY

Before discussing the gross and microscopic approaches to thyroid pathology, the use of frozen section in the intraoperative setting needs to be addressed. In the modern era, with the extensive use of preop FNA and more recently molecular testing, the diagnosis of a thyroid nodule is known in up to 70% of cases. For those 30% that are



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"indeterminate", assessment of the nodule by frozen section is often fruitless. Diagnoses such as "follicular lesion", or "follicular proliferation" do not disclose if a nodule is benign or malignant and cannot guide immediate therapy or change surgical approach. In addition it adds time and cost to the procedure and in certain instances may lead to an incorrect diagnosis (both false positive and false negatives may occur); confusion may also exist with post biopsy changes leading to overdiagnosis of invasion. In addition, frozen section introduces nuclear artifact which may hamper optimal evaluation on permanent sections. These issues may result in inappropriate treatment in the intraoperative setting. We strongly recommend that the primary intrathyroidal nodule not be subjected to frozen section (of course, frozen sections may be used to assess nodes for possible metastases, identification of parathyroids, or extrathyroidal soft tissue extension by tumor).

MACROSCOPIC APPROACH TO THYROID SPECIMENS:

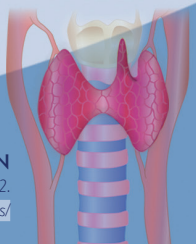
1. The surgically resected specimen should be received intact and in the unfixed state by the pathologist.
   a. The intact specimen should be inked with commercially available inks which remain adherent to the tissue through various steps of processing.
   b. Some surgeons are interested in identification of margins which might appear microscopically involved by tumor; hence pathology laboratories distinguish posterior from anterior thyroid areas by painting these with different colors of ink.
2. The specimen should be weighed and measurements are taken in three dimensions.
   a. The size of each lobe and the isthmus should be documented. Whether or not a pyramidal lobe is present should be noted.
   b. Care should be taken to examine for the presence of peri-thyroidal lymph nodes or parathyroid glands or separate tissue fragments thereof.
   c. The presence of nodules identified in the intact specimen and the laterality should be noted. If available gross photography of the specimen is recommended.
3. The specimen should be sectioned.
   a. There is no recommended standard approach to dissecting a thyroid specimen with nodules.
   b. Most pathologists prefer bisecting the lobe or area of the thyroid with the nodule in a perpendicular plane. Thus the lesion could be recognized, its capsule identified and measured and the characteristics of the nodule described to the presence of cysts, hemorrhage, necrosis or calcification.
   c. If available, gross photography of the lesion(s) is recommended.
4. The specimen should be fixed (neutral buffered formalin is the standard) for at least 10 and preferably 24 hours before sections are taken.
5. Sectioning of the specimen should be concentrated on the dominant or solitary nodule especially if it is encapsulated.
   a. If the lesion is grossly infiltrative this should be documented by appropriate sectioning of these areas of infiltration.
   b. In totally encapsulated nodules it is recommended that if the nodule measures 2.5 cm or less the entire nodule with its capsule be submitted for microscopic examination.
   c. In those encapsulated nodules which are larger, generous sampling of the tumor capsule thyroid interface is recommended. The older literature suggested at least 10 blocks from the region of the capsule be submitted (these blocks can contained 2-3 portions of the capsule tumor interface each). In the event that microscopic examination of these initial sections is worrisome, additional sectioning from the gross specimen and also deeper sections from the worrisome blocks is strongly suggested.
   d. In many modern pathology practices, the entire capsule-tumor-thyroid interface is submitted for histological examination. Invasive foci are often focal and may be missed if only representative sections are taken.
6. Tissue sections of nodular lesions representing the relationship between the nodule and the thyroid edge (margin) is recommended in order to assess for extrathyroidal extension and adequacy of surgical margins.
7. Sectioning of thyroid glands removed for diffuse disease such as chronic lymphocytic thyroiditis or Graves' disease and in which gross examination shows no nodular areas, is usually predicated based on gland weight. Many pathology practices recommend one block of tissue for every 10g of weight of the specimen.
8. It is of course important to representatively and randomly sample "normal looking" thyroid.

MICROSCOPIC EVALUATION OF THE THYROID SPECIMEN

It is beyond the scope of this document to describe the histologic report for every possible thyroid diagnosis and lesion. In terms of quality control, certain common features which are necessary for the final pathology report are discussed.

The nature of the thyroid disease. If it is diffuse disease such as chronic lymphocytic thyroiditis or Graves' disease, the diagnosis is straightforward. If there is a nodule than it must be determined if the nodule is benign or malignant. If it is malignant the subtype of tumor should be identified.

1. ***Benign nodules*** are most often follicular adenomas or adenomatous or hyperplastic nodules.
2. ***Malignant lesions*** are most frequently of epithelial origin; that is, carcinomas. Of these, those of follicular derivation (papillary carcinoma and its variants, follicular carcinoma, Hürthle cell carcinoma, poorly differentiated and anaplastic carcinoma) are most frequent.



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a. *Papillary thyroid carcinoma* is the most common type of epithelial malignancy of the thyroid and of the entire endocrine system. It makes up about 85% of all thyroid carcinomas. The final pathology report on a papillary thyroid carcinoma should identify the subtype (major type and if present any minor component of a different subtype), the size of the lesion and location, the presence of psammoma bodies or viable tumor in nontumoral thyroid lymphatics, the presence of vascular invasion, perineural invasion, and whether or not the lesion shows extrathyroidal extension.

b. *For follicular, Hürthle cell or oncocytic and poorly differentiated carcinoma*, in addition to tumor size and site, the presence of capsule should be noted as should be calcification in the tumor and/or the capsule, the presence of invasion into the capsule or through the capsule, the presence of vascular invasion in the capsule or vascular invasion in the surrounding thyroid or extra-thyroidal tissues.

3. *For medullary thyroid carcinoma*, tumor size and site and histologic subtype should be noted. The presence of multifocality and the identification of C cell hyperplasia in the nontumoral thyroid is important. The latter may require immunostain for calcitonin to identify C cell proliferations. The identification of lymphatic, vascular, or peri-neural invasion should be noted.

4. *Anaplastic thyroid carcinomas* usually have been preoperatively diagnosed by FNA or small biopsies. These tumors may be resected for palliative or other purposes. In some of these resection specimens anaplastic carcinoma may be associated with a differentiated tumor. In these cases, providing the percent of anaplastic carcinoma as a ratio of its relationship to the entire tumor mass may be of interest, since there is some low quality evidence that anaplastic carcinomas making up 25% or less of the thyroid tumor that is otherwise differentiated may do slightly better prognostically.

5. *Examination of lymph nodes*.

a. Many specimens of thyroidectomy performed for known or suspicious carcinoma, especially papillary type, contain tissue from the central compartment of the neck (level VI lymph nodes).

b. Some cases in which enlarged lateral nodes are present also contain sampling of lateral neck nodes (usually levels III-V). The prosector should dissect all nodes or nodules suspected to represent nodes and submit these for histologic processing.

c. The pathologist should evaluate the number of nodes recovered from the specimens, the number of nodes involved by metastatic disease, size of the largest involved node and the largest metastatic focus, and examine for extranodal extension. (The interobserver variability in the assessment of extranodal extension in papillary thyroid carcinoma is quite wide and clinicians should be aware of this challenge in pathology interpretation.)

6. *The issue of extrathyroidal extension*.

a. Extrathyroidal extension of tumor, usually in papillary carcinoma, is another problematic area in pathologic interpretation of thyroid cancer specimens. There are several reasons for this, including the fact that certain areas of the thyroid are unencapsulated or devoid of a true capsule (such as the region of the isthmus and posterior aspects of thyroid gland). Where the thyroid gland actually ends and extrathyroidal soft tissue begins can be impossible to determine.

b. Not infrequently, thyroid papillary carcinomas, especially microcarcinomas, can arise close to the edges of the thyroid gland and show what appears to be involvement of perithyroidal adipose and/or soft tissue. In the previous staging system (AJCC 7th edition) such minimal extrathyroidal extension was considered stage III disease.

c. In the latest staging system (AJCC 8th edition), stage III disease requires gross extrathyroidal extension to skeletal muscle in the neck. Although as yet, no formal studies are available, it seems that this newer system may be easier to use leading to improved interobserver variability.

7. For the most common thyroid carcinoma (papillary thyroid carcinoma) some pathology reports include a standard diagnostic terminology which can be incorporated as an expedited diagnosis in any laboratory information system. At our institution the following is used:

Papillary thyroid carcinoma,–variant,–cm, encapsulated/unencapsulated, with/without capsular invasion, with/without intralymphatic psammoma bodies in nontumoral thyroid parenchyma, with/without angioinvasion. Tumor is confined to the thyroid gland or tumor shows extrathyroidal extension.

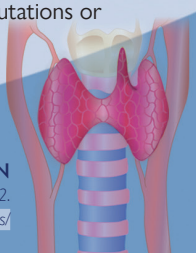
This particular diagnostic paragraph was developed in conjunction with our surgical and endocrinologist colleagues so that the initial diagnostic portion of the report contains in abbreviated form the most important information regarding a particular diagnosis of papillary thyroid cancer. The synoptic summary is included at the bottom of the report.

8. *Most pathology laboratories utilize a synoptic reporting system* when issuing pathology reports on cancer specimens of various organs.

a. Some of these systems are "home grown"; many laboratories however utilize the synoptic reporting schema defined by the College of American Pathologists (CAP); these are updated approximately every 5 years by a panel of experts in thyroid cancer, and incorporate new information especially with regard to staging systems and newer pathologic entities. In recent years where appropriate, the integration of molecular testing into the pathology report is also included.

9. *Thyroid carcinoma and molecular testing*.

a. Over the past years, molecular testing has become an important tool in thyroid nodule management. Most of this type of testing is performed on fine needle aspiration material to risk-stratify indeterminate nodules, and less frequently, to provide prognostic information. (It is beyond the scope of this document to describe the various types of testing and the genetic mutations or translocations).



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WHEN TO SEEK CONSULTATION

1. There are cases of thyroid tumors that, by their nature, present difficulty for the practicing pathologist. There are areas with some subjectivity to their diagnosis and hence high interobserver variability. These include the distinction between noninvasive follicular thyroid neoplasm with papillary like nuclear features vs encapsulated follicular variant of papillary carcinoma; the assessment of invasion in follicular thyroid tumors; post biopsy pseudo-invasion artifact; and C cell proliferations, to name a few.
2. It is important to assess preoperative biopsies with as specific a diagnosis as possible. Even molecular testing may not be absolutely definitive in distinguishing benign from malignant nodules. The extent of surgery will depend therefore on the preop diagnosis. So it is recommended that, even at this stage in the approach to thyroid nodules, a second expert opinion should be sought for challenging cases.
3. After the surgical removal of the thyroid, the diagnosis may be made but certain tumor features which may lead to different postoperative therapy or to prediction of prognosis may still be uncertain. These are questions such as: is there vascular invasion; is there extraglandular extension; is there a proliferation of C cells? In such cases, and cases where the tumor diagnosis is in question, consultation may be helpful.

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FURTHER INFORMATION

For more information on the survey findings, see *Thyroid, Vol. 27, No. 12.* https://www.thyroid.org/professionals/ata-publications/