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Atlas of Thyroid Cytopathology

With Histopathologic Correlations
Visit our website at www.demosmedpub.com

ISBN: 9781933864952

Acquisitions Editor: Rich Winters
Composer: diacriTech

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Library of Congress Cataloging-in-Publication Data
Ali, Syed Z., author.
p. ; cm.
Includes bibliographical references and index.
I. Nayar, Ritu, author. II. Krane, Jeffrey F., author. III. Westra, William H., author. IV. Title.
[DNLM: 1. Thyroid Diseases—diagnosis—Atlases. 2. Thyroid Diseases—pathology—Atlases. 3. Cytodiagnosis—Atlases. WK 17]
RC655
616.44—dc23
2013025694
Contents

Contributors vii
Foreword ix
Preface xi

1. Thyroid Fine Needle Aspiration Biopsy: General Considerations 1
   Zubair W. Baloch

2. Radiologic Characteristics of Thyroid Disease 9
   Ulrike M. Hamper

3. Nonneoplastic Nodules and Cysts 31

4. Atypia of Undetermined Significance (AUS)/Follicular Lesion of Undetermined Significance (FLUS) 55

5. Follicular Neoplasm/Suspicious for a Follicular Neoplasm 65

6. Hürthle Cell Neoplasm/Suspicious for a Hürthle Cell Neoplasm 89

7. Suspicious for Malignancy 101

8. Papillary Thyroid Carcinoma and Variants 109

9. Medullary Thyroid Carcinoma 143

10. Poorly Differentiated Thyroid Carcinoma 159
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>Undifferentiated (Anaplastic) Carcinoma and Squamous Cell Carcinoma of the Thyroid</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td><em>Armanda Tatsas</em></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Rare Primary Carcinomas and Mesenchymal Neoplasms</td>
<td>185</td>
</tr>
<tr>
<td>13.</td>
<td>Metastatic and Secondary Cancers</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td><em>Index</em></td>
<td>213</td>
</tr>
</tbody>
</table>
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With this atlas of thyroid cytopathology and histopathology, Drs. Ali, Nayar, Krane, and Westra have provided a valuable tool for cytologists learning (and continuing to learn) fine needle aspiration (FNA) cytology of the thyroid. The authors beautifully illustrate the wide variety of lesions that can be encountered, from the commonplace benign follicular nodule to the rarest of thyroid neoplasms.

This atlas follows a logical outline, adhering to the categories of The Bethesda System for Reporting Thyroid Cytopathology, widely used in the United States and elsewhere for reporting the results of thyroid aspiration biopsies. This makes the content immediately easy to follow, as the authors weave a path from benign nodules to cases that are atypical or suspicious, ending with unequivocally malignant neoplasms.

The authors include a wide variety of sample preparation methods—smears, liquid-based preparations, and cell blocks—as well as the commonly used stains—Papanicolaou, Romanowsky, and hematoxylin & eosin—providing the reader with the greatest flexibility in recognizing cytomorphic patterns. Relevant immunocytochemical stains are included for good measure.

Ultimately, however, it is the juxtaposition of histopathologic and cytologic images that makes this book so valuable. In many cases, the caption headings of the cytologic images reflect a retrospective diagnosis based on histologic follow-up. The text is careful to point out, for example, that it is rarely possible to make a definitive diagnosis of a poorly differentiated carcinoma of the thyroid on a fine needle aspiration sample. The same applies to adenomatoid nodules, follicular adenoma, follicular carcinoma, and a variety of other less common entities. Histologic correlation is an excellent teacher, but limitations to cytologic classification remain, and the reader must learn to report cytologic findings using cytologic, not histologic terminology.

This book, with its beautiful images illustrating thyroid cytologic-histologic correlation, provides the ammunition a cytologist needs to master thyroid FNA interpretation.

Edmund S. Cibas, MD
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This atlas is published at an exciting time for the diagnosis of thyroid disease by cytopathology. Thyroid fine needle aspiration in conjunction with ultrasonographic imaging has transformed the management of clinically frequent thyroid nodules. More recently, and with significant contributions by the authors of this atlas, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), has provided unifying terminology in the United States and elsewhere for the reporting of thyroid aspirates. Among the strengths of TBSRTC framework are the associations of defined risks of malignancy and expected management approaches with each of the six major diagnostic categories.

At the same time, we must acknowledge that there remain significant challenges and limitations in the recognition of thyroid cancer sonographically, cytologically, and histologically. Cytomorphologic evaluation on fine needle aspiration remains to date the initial diagnostic modality of choice for a patient with a thyroid nodule and hence we all have witnessed an “epidemic” of thyroid aspirations in our practices. Surgical follow-up of indeterminate cytologic diagnoses most frequently yields benign histologic outcomes revealing the need for improved triage of patients for surgery. Additionally, the ability to diagnose smaller, incidental thyroid cancers in this typically indolent disease poses important dilemmas about which nodules to image and sample cytologically and in determining who needs surgery, what the extent of surgery should be, and for whom additional treatment, such as radioiodine therapy, is appropriate. Accordingly, there is tremendous interest and excitement regarding the potential role of molecular testing both for resolving diagnostic uncertainty and for refining clinical management. As yet, however, consensus regarding appropriate and cost effective use of this promising tool remains a goal rather than a reality.

Solutions to these difficult questions will require interdisciplinary cooperation amongst endocrinologists, surgeons, radiologists, cytopathologists, and surgical pathologists. This atlas embraces the importance of an interdisciplinary approach and is intended to capture our current state of knowledge for diagnosing thyroid nodules by ultrasound imaging, fine needle aspiration cytology, and gross and histologic evaluation of surgical pathology specimens. It is our sincere hope and belief that the quantity and quality of the images included herein will provide the reader with valuable and practical insights into the current state of the art in this rapidly evolving field and will further enrich the knowledge and learning acquired since the publication of TBSRTC.

Syed Z. Ali
Ritu Nayar
Jeffrey F. Krane
William H. Westra
Thyroid Fine Needle Aspiration Biopsy: General Considerations

Zubair W. Baloch
Thyroid nodules are common and have been affecting human kind since ancient times. They can be seen in artworks and artifacts of many cultures. Though, in the current era iodine supplementation has greatly reduced the number of thyroid enlargements, epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world. In contrast, high resolution ultrasound (US) can detect thyroid nodules in 15% to 67% of the population with higher frequencies in women and the elderly [1–3]. The main purpose of thyroid nodule evaluation is to exclude thyroid cancer which is seen in 5% to 10% of cases requiring surgical intervention. It has been shown that the prevalence of thyroid nodularity and thyroid cancer is related to age, gender, radiation exposure history, family history of thyroid carcinoma in first degree relative, and other factors such as rapid growth and hoarseness [1,4–6]. The follicular cell derived—well-differentiated thyroid cancer, that is, papillary and follicular carcinoma, comprises the vast majority (90%) of all thyroid cancers. According to the recent figures 44,760 new cases of differentiated thyroid cancer were diagnosed in 2010 which resulted in death in 1,690 patients. It is projected that these numbers may be increasing in the future. Furthermore, 2 out of 3 cases are found in people with an age range of 22 to 55 years [7,8].

**EVALUATION OF THYROID NODULES**

**Clinical Evaluation**

Thyroid nodule is a discrete lesion within the thyroid gland which appears distinct from the surrounding thyroid parenchyma either by palpation or on ultrasound examination. Most sizeable thyroid nodules are palpable except the ones situated in the posterior aspect of the thyroid lobes. Ultrasound evaluation of the thyroid gland can detect many nonpalpable thyroid nodules of all sizes and shapes; often termed as “incidentalomas.” It has been shown that the risk of malignancy is similar between palpable and incidentally discovered thyroid nodules [1,9]. Initially, it was thought that a solitary thyroid nodule is more prone to harbor malignancy as compared to those seen in the setting of multinodular goiter; however, several authors have proven by studying large case cohorts that risk of malignancy is the same in solitary vs. multiple nodules [10,11]. According to the American Thyroid Association the initial evaluation of all patients with thyroid nodules should include serum thyrotropin (TSH) level determination followed by radionuclide imaging if it is suppressed to exclude a hyperfunctioning (AKA hot) nodule [1]. It is prudent that the cytopathologists should be made aware of or obtain this data since the functional status of the thyroid or that of the biopsied nodule affects the cell morphology seen in cytologic specimens. For example evidence of chronic lymphocytic thyroiditis and oncocytic metaplasia in hypothyroid and presence of random nuclear enlargement and atypia in hyperthyroid patients and hyperfunctioning (toxic) nodule(s) [12,13]. The other laboratory tests performed as part of a pre-fine-needle aspiration (FNA) panel include serum thyroglobulin and calcitonin measurements; these are not practiced routinely in the United States.

**Ultrasound Evaluation**

It is recommended that thyroid ultrasound be performed in all patients found to have solitary or multiple thyroid nodules to define the anatomical detail, structure, and the exact extent and location of true nodule(s) [14–17]. Many clinicians who employ thyroid ultrasound also use it as an adjunct to their physical examination. Multiple nodules palpated in Hashimoto thyroiditis may not correlate with the nodule reported on ultrasound thus avoiding biopsy of multiple nodules. The ultrasound features that are suspicious for malignancy include micro-calcifications, marked hypo-echogenicity, an irregular or micro-lobulated margin, a longitudinal dimension larger than the cross sectional dimension, intrinsic vascularity, and direct tumor invasion of adjacent tissue. Neck ultrasound in patients with suspicious thyroid nodules can be helpful in detection of abnormal vs. benign lymph nodes to assess the extent of disease for proper surgical management [15,18,19]. Though ultrasound is more sensitive than clinical and laboratory evaluation of a patient with nodular enlargement of the thyroid it is a poor predictor of malignancy. For
example, hypoechoic thyroid nodules are more likely to be malignant; however, most benign nodules are also hypoechoic [14,15].

At present besides its few aforementioned uses ultrasound is commonly employed to guide the FNA biopsy needle to obtain adequate diagnostic material from a thyroid nodule.

**Fine-Needle Aspiration Biopsy**

Fine-needle aspiration biopsy (FNAB) of the thyroid has now been established as reliable and safe and has become an integral part in the management of thyroid nodules. Based on the examination of a few groups of cells it can effectively triage cases which require clinical or surgical follow-up.

**Procedure**

Thyroid FNAB can be performed manually by palpation or employing ultrasound guidance. It is recommended that FNAB is performed by a clinician, radiologist, or pathologist who is proficient/experienced in thyroid FNAB [20]. The use of ultrasound guidance ensures that the sample is obtained from the nodule in question and allows directing the needle into the solid portions of a complex solid and cystic nodule, thus improving the diagnostic yield [14,20]. The specimen should be obtained using either a 25 or 27-gauge needle which can be either attached or not (non-aspiration technique) to a syringe; however, the former method is the most favored one. The correlation between the gauge of the needle and the cellularity of the specimen has been discussed in the literature [21]. A higher rate of specimen adequacy has been reported with a thinner gauge needle. Various studies have compared FNAB of thyroid by employing aspiration and non-aspiration (capillary action) techniques. Some authors have shown no difference between the two sampling techniques while others have reported a higher rate of adequacy with non-aspiration technique. In any event this is highly dependent upon the preference and experience of the operator with either technique [21–24]. Multiple passes in a thyroid nodule may not prove to be useful in acquiring adequate cellularity as thyroid nodules are inherently vascular and lead to increased bleeding resulting in diluted specimen [22,25].

**Specimen**

It is well understood that the precise and management based cytologic diagnosis is highly dependent upon an adequate specimen with well-preserved cellular details. Therefore, regardless of the cytologic preparation, that is, smears, cytopspins, monolayer preps, and cell block, an adequate and well-preserved thyroid FNAB specimen is important for rendering cytologic interpretation [26–29]. Many experts have proposed various criteria for cell adequacy in thyroid FNAB specimens [30–33]; it is well understood that these criteria of adequacy apply to solid nodules, solid and cystic nodules and not to cystic nodules with no solid component on ultrasound evaluation. The most commonly used criterion for specimen adequacy is: six to eight groups of follicular cells with 10 to 20 cells per group on two different slides. Adequate cellularity of a thyroid FNAB specimen reflects adequate and representative sampling of the nodule; granted, this is highly operator dependent [33]. In my experience an adequate and representative thyroid FNAB specimen is acquired by using ultrasound-guidance and making sure that the biopsy needle samples multiple rather than one portion of the nodule.

**On-Site Evaluation**

The on-site evaluation of thyroid FNAB specimens with performance of rapid stains leads to adequate specimens and lessens nondiagnostic rates; however, this may not be possible in all clinical settings. The clinical utility of the on-site assessment of thyroid FNA is similar to the interpretation of frozen sections in surgical pathology. A number of questions can be answered by on-site evaluation, which include adequacy of specimen, classification of lesion, primary vs. metastatic, and if additional studies are needed (flow cytometry, serum calcitonin measurements to rule out medullary carcinoma and molecular studies) [25,34,35].

The number of on-site smears should be kept low, 2 to 3 smears/pass; they can be air dried for Romanowsky stain or fixed in 95% alcohol or spray fixed for Papanicolaou stain. The Romanowsky staining method is one of the best available methods for immediate evaluation of FNA specimens; however, some authors have proposed the rapid Papanicolaou
staining method. Papanicolaou stain is vital to the diagnosis of thyroid lesion. It effectively highlights the nuclear details and alterations (grooves and inclusions), which are crucial for the diagnosis of papillary thyroid carcinoma. It also is helpful in the diagnosis of Hürthle cell and C-cell lesions. If one is not providing on-site assessment then an FNAB specimen can be placed into an appropriate medium for monolayer preparation (ThinPrep®, SurePath®, etc.) or other concentration techniques and preparations [25].

It is well established now that molecular testing can serve to further refine the cytologic interpretation. Therefore, a portion or an entire thyroid FNAB pass maybe processed for molecular diagnosis. This is highly dependent upon the molecular test(s). In case of BRAF mutational analysis DNA can be extracted from the FNAB material in routinely air-dried smears or leftover needle rinse, however, mutational analysis for multiple genes will require a dedicated FNAB pass stored at −80°C [36].

### Core Needle Biopsy

Although, FNAB is the most commonly employed method for obtaining diagnostic material from a thyroid nodule, in some cases it may not yield sufficient diagnostic material even with multiple passes and repeat procedures. It has been shown that core biopsy (18–20 gauge needle) can increase the diagnostic yield by 10% as compared to FNA. The core biopsy does provide a large amount of histologic material to be examined for evaluation of cytologic as well as architectural features; however, the success of this procedure is highly dependent upon the operator being well versed in this procedure as there is also an increased risk of complications such as hematoma formation [25, 37, 38].

### Diagnostic Classification

Thyroid FNA specimens are usually classified by employing a tiered system. Several classification schemes have been proposed by various authors based on personal/institutional experiences. In 2007, the National Cancer Institute hosted a two day state of the art scientific meeting regarding thyroid fine needle aspiration. The participants included endocrinologists, radiologists, surgeons, and pathologists. This meeting led to various position statements on the selection of patients for thyroid biopsy, handling of thyroid FNA specimens, and their cytopathologic diagnosis. At this conference many participants agreed to a six-tiered scheme for classifying thyroid FNAs (Table 1.1). Each diagnostic category was assigned a risk

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
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</thead>
<tbody>
<tr>
<td>Nondiagnostic or unsatisfactory</td>
<td></td>
<td>repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0%–3%</td>
<td>clinical follow-up</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>-5%–15%</td>
<td>repeat FNA</td>
</tr>
<tr>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>15%–30%</td>
<td>surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60%–75%</td>
<td>near-total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97%–99%</td>
<td>near-total thyroidectomy</td>
</tr>
</tbody>
</table>

Table 1.1 — The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management [39,40,41]
of malignancy based on literature review along with recommenda-
tions for management. It is also recommended that for some of the diagnostic categories, some degree of sub categori-
ization can be informative and is often appropriate. Additional descriptive comments (beyond such sub categorization) are optional and left to the discretion of the cytopathologist [39,42]).

The brief description of the diagnostic categories in the Bethesda Classification is as follows:

I. Nondiagnostic or Unsatisfactory:
   a. This diagnostic category applies to specimens which are nondiagnostic due to limited cellularity, no follicular cells and adequate specimens which are uninterpretable due to poor fixation and preservation, that is, obliteration of cellular details.
   b. In some cases of solid nodules it may be prudent to process and examine the entire specimen.
   c. It is recommended that solid nodules with repeat nondiagnostic FNA results should be excised because malignancy is eventually diagnosed in about 9% of such cases.

II. Benign:
   a. The reported rate of malignancy for this diagnostic category is 0% to 3%
   b. The diagnostic terms in this category include, but are not limited to, nodular goiter, hyperplastic/adenomatoid nodule in goiter, chronic lymphocytic thyroiditis and sub-acute thyroiditis.
   c. A thyroid nodule with a benign diagnosis should be followed periodically by US examination; a repeat FNA may be considered if the nodule increases in size (as per American Thyroid Association (ATA) guidelines the increase should be in 20% in two dimensions of the nodule; and that of solid component in case of cystic nodules).

III. Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS):
   a. The literature review of the large cases series published after Bethesda classification scheme shows that this represents a heterogeneous diagnostic category (a true Gray Zone).
   b. The reported malignancy risk for cases diagnosed as such in these studies ranges from 6% to 48% [43–45].
   c. It is recommended that the number of cases diagnosed as such should be kept to a minimum; 7% of the total diagnoses. The question arises what can serve as a guide for keeping the AUS/FLUS diagnosis in an acceptable range. One obvious answer is to use the AUS/FLUS:malignant diagnoses ratio similar to ASCUS:SIL ratio in cervical cytology, however, this needs to be proven by independent studies from multiple institutions.
   d. It has been shown that repeat FNA is effective in arriving at definite management based diagnosis in thyroid nodules initially diagnosed as indeterminate. Therefore, repeat FNA should be recommended in cases diagnosed as AUS/FLUS. It is clearly evident that repeat fine needle aspiration (RFNA) has a definite role in the management of patients with thyroid nodules diagnosed as FLUS/AUS.

IV. Follicular/follicular neoplasm with oncocytic features (AKA Hürthle cell) neoplasm or suspicious for follicular or follicular neoplasm with oncocytic features (AKA Hürthle cell) neoplasm:
   a. These diagnostic terms encompasses both benign and malignant tumors; that is, follicular adenoma and carcinoma and oncocyic follicular adenoma and carcinoma. The cytologic diagnosis of “neoplasm” reflects the limitations of thyroid cytology, since the diagnosis of follicular carcinoma is only based on the demonstration of capsular and/or vascular invasion. Several authors have shown that, at most, only 20% to 30% of cases diagnosed as “follicular neoplasm” are diagnosed as malignant on histological examination and the rest are either follicular adenomas or cellular adenomatoid nodules, that is, benign.
   b. Several studies have shown that half or more of the malignant cases diagnosed as follicular neoplasm or
suspicious for follicular neoplasm (FON/SFN) are found to be follicular variant of papillary thyroid carcinoma (FVPC) on surgical excision. It is well-known that the surgical pathology diagnosis of FVPC (the so called “Gold Standard”) can be problematic even for experts due to multifocal rather than diffuse distribution of nuclear features of papillary carcinoma. Thus, the sampling of the areas lacking diagnostic nuclear features is the main reason for the under-diagnosis of these cases as SFN/FON.

V. Suspicious for malignancy:

a. This term includes suspicious for: papillary carcinoma (malignancy risk 60%–75%), medullary carcinoma, other malignancies, lymphoma (flow cytometry can be recommended with repeat FNA), metastatic carcinoma/secondary tumor and carcinoma (includes poorly differentiated and anaplastic carcinoma).

VI. Malignant:

a. The thyroid FNA cases diagnosed as such carry a 97% to 100% risk of malignancy. The malignant tumors of the thyroid diagnosed on FNA include: papillary carcinoma and variants, medullary carcinoma, poorly differentiated carcinoma, anaplastic carcinoma, metastatic carcinoma/secondary tumor and carcinoma (includes poorly differentiated and anaplastic carcinoma).

Bethesda Thyroid FNA Classification Across Atlantic

The United Kingdom Royal College of Pathologists has recommended a tiered diagnostic classification scheme based on the similar needs which led to the formulation of Bethesda Thyroid FNA Classification. Basically, this scheme has adopted all the diagnostic categories with altered names to incorporate the “British Thy terminology” designations. This has also led the European cytopathologists to consider the need for a standard scheme for reporting thyroid FNA specimens similar to Bethesda terminology. Therefore, it is not bold to forecast that in the near future Bethesda terminology or ones similar to it will be adapted to meet the needs of diagnosing thyroid nodules in different parts of the world [46,47].

Reflex Molecular Testing of Thyroid FNAB Specimens

Similar to other organ systems new perspectives for reclassification and diagnosis of thyroid tumors especially papillary and follicular carcinoma have emerged based on identification of somatic mutations. At present there is a dearth of information regarding molecular analyses of thyroid FNA specimens for BRAF gene mutation, RET/PTC translocation, PAX8-PPRA-gamma, and RAS-gene mutations. As mentioned previously thyroid FNA cannot differentiate between follicular adenoma and carcinoma and in this a majority of FNA samples obtained from follicular variant of papillary carcinoma are classified as follicular neoplasm or suspicious for papillary thyroid carcinoma due to paucity of the diagnostic features. Based on the molecular data available several authors have used one or all of the above-mentioned markers to diagnose papillary and follicular thyroid carcinoma in FNA specimens. These studies have shown much promise with high positive predictive value of malignancy. This role of molecular markers as an adjunct to the cytopathologic diagnosis of thyroid nodules is growing at a speedy rate. Therefore, “reflex” molecular testing of thyroid FNA specimens diagnosed as AUS/FLUS, FON/SFN, and suspicious for papillary carcinoma is considered as standard practice by many laboratories [48–51].

REFERENCES


