Management of Thyroid Nodular Disease

Current Cytopathology Classifications and Genetic Testing

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KEYWORDS

• Thyroid nodules • Molecular markers • Genetic testing • Bethesda classification • Afirma

KEY POINTS

- The Bethesda system for reporting thyroid cytopathology provides a standardized method of reporting results from fine-needle aspiration of thyroid nodules.
- The Bethesda system for reporting thyroid cytopathology should be applied universally to improve communication between pathologists and clinicians.
- For patients with indeterminate cytology, the Afirma gene expression classifier and tests for genetic mutations may provide helpful diagnostic and prognostic information with which to optimize treatment plans.

INTRODUCTION: NATURE OF THE PROBLEM

Thyroid nodules are common. Reports in the literature suggest a prevalence of 4% to 76% in the general population, depending on the mode of detection and the population studied.[1–3] Autopsy studies have reported similar prevalence rates.[4,5] Increased use of ultrasound technology has led to increased detection of thyroid lesions over the last 30 years.[5–7]

Most thyroid nodules are benign, with only 5% to 10% representing a malignant tumor.[7–11] Evaluation for thyroid malignancy is necessary after the discovery of many thyroid nodules to determine appropriate management recommendations. Nodules greater than 1 to 1.5 cm in size or associated with abnormal lymph node(s) on

The authors have nothing to disclose.

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Surg Oncol Clin N Am 25 (2016) 1–16
http://dx.doi.org/10.1016/j.soc.2015.08.001 **surgonc.theclinics.com**
1055-3207/16/$ – see front matter

ultrasonography should receive an ultrasound-guided fine-needle aspiration (FNA) to obtain a sample for cytologic evaluation of malignancy.[3,12]

The clinical utility of FNA to guide management decisions occurs when results clearly indicate benign or malignant disease. However, FNA is not a perfect diagnostic tool. Variation in the interpretation of cytopathologic samples can occur between pathologists and across institutions,[13] leading to controversy over management. Moreover, approximately 10% to 25% of FNA evaluations report "indeterminate" results whereby neither benign nor malignant disease can be declared.[3,14] Consequently, thyroid lobectomy is needed to obtain tissue for an accurate diagnosis. However, more than half of these patients are found to have benign disease on formal pathologic evaluation, making their surgery seem unnecessary.[15] For those with malignancy found on surgical pathology, a second operation is usually recommended to improve surveillance for recurrence and to permit additional treatment when necessary. The need for a second operation can be troubling for patients and challenging for surgeons.[16]

Improved characterization of thyroid nodules is necessary to guide appropriate patients to surgery and reduce unnecessary surgeries. A universal cytopathologic classification system and several diagnostic tests have been developed in the last decade to facilitate the decision-making process.

CYTOPATHOLOGIC CLASSIFICATION

Bethesda Classification System

Background

Before 2007, multiple classification systems existed describing the results of FNA of thyroid nodules. Discordance between these classification systems led to inconsistent reporting of FNA results, creating confusion among clinicians and limiting the effectiveness of the test.[17,18] At the National Cancer Institute conference in the fall of 2007, a leading group of pathologists and clinicians proposed a 6-tiered classification scheme,[19] known as The Bethesda System for Reporting Cytopathology ("the Bethesda system"). The goal of the system was to provide a consistent means of reporting clinically relevant information so that physicians could best advise patients[17] (**Table 1**).

The classification system

A description of each category follows, along with the clinical recommendations put forth by the Bethesda group. Similar information is available in **Table 1** for ease of review. The chart is designed to be printed and posted in the surgical office setting, and can be especially helpful in an academic setting to raise awareness of the standard of care and encourage appropriate treatment decisions.

Class I: nondiagnostic or unsatisfactory FNA samples may have blood obscuring the specimen, a thick smear, smears that are improperly dried, or an insufficient quantity of cells.[17] The malignancy risk in nondiagnostic or unsatisfactory samples is 1% to 4%. Repeated aspiration of the nodule with ultrasound guidance should lead to a diagnostic result in 50% to 88% of cases; for nodules that remain nondiagnostic or unsatisfactory after repeat aspiration, excisional biopsy leads to a malignant result in 10%.[17] *Recommendation:* Repeat FNA under ultrasound guidance is suggested.

Class II: benign Thyroid FNAs are benign in 60% to 70% of cases. The false-negative rate of a benign result is 0% to 3%. Patients with a benign FNA should be followed clinically for 6 to 18 months, and repeat ultrasound, FNA, or both performed if clinical changes are noted.[17] *Recommendation:* Ultrasonographic surveillance every 6 to 18 months to assess stability. Change warrants repeat FNA.[12]