Ancillary Studies in Thyroid Cytopathology

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KEYWORDS

• Thyroid • Neoplasm • Molecular pathology • *BRAF* • *RAS* • *RET/PTC* • *PAX8/PPARγ* • *Veracyte* • *Afirma*

ABSTRACT

Recent advances in thyroid imaging, clinical evaluation, cytopathology, surgical pathology, and molecular diagnostics have contributed toward greater understanding of thyroid nodules. In particular, the development of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) has brought standardization to the field and the system dovetails well with the implementation of immunohistochemistry and molecular testing to diagnostic practice. Among the molecular strategies available, the application of the molecular panel of common genetic alterations can stratify indeterminate BSRTC diagnoses into low-risk and high-risk groups. The molecular panel markers have a high positive predictive value and therefore, the panel is considered to be a "rule-in" test. In contrast, the Afirma gene expression classifier by Veracyte Corporation is a test that has been reported to have a high negative predictive value, and therefore, considered to be a "rule-out" test. With further advances, refinements are expected to be made. In particular, the application of next-generation sequencing technology holds promise in bringing thyroid cytopathology to the next level.

OVERVIEW

Fine needle aspiration (FNA) cytology has proven to be an effective method for collecting material that provides characteristics of thyroid nodules and estimates the risk of malignancy. Over recent decades, refinements have been made in imaging, localization of lesions, sampling technique, specimen processing, standardized reporting, and application of ancillary studies. In particular, advances in thyroid molecular testing have taken place in parallel with the implementation of a standardized reporting system for classifying thyroid FNA samples: the Bethesda System for Reporting Thyroid Cytopathology (BSRTC).[1,2] In this review, we provide an overview of how recent developments in clinical molecular testing have impacted the evaluation of thyroid nodules. First, we discuss the common differential diagnoses associated with the BSRTC categories. Then, we focus on the application of ancillary testing to thyroid cytopathology, in particular the use of immunohistochemistry (IHC) and molecular testing in common follicular-derived thyroid neoplasms. Recent correlation studies have shed light on the association of BSRTC diagnoses with certain molecular alterations and outcome. This knowledge provides powerful insight into predicting the nature of the thyroid nodule. However, to determine the best management strategy from the cytopathologic and molecular information, the findings should be interpreted in the appropriate context to avoid pitfalls. Finally, we mention some technologies that may influence future trends in this area.

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DIFFERENTIAL DIAGNOSIS ASSOCIATED WITH BSRTC CATEGORIES

One of the main challenges in thyroid cytopathology stems from the fact that a significant proportion of malignancies are low-grade follicular-derived carcinomas with cytopathologic features that overlap with benign hyperplastic or neoplastic nodules.[3] Furthermore, thyroid FNAs have a low pretest probability of malignancy (approximately 5%–10%). These features contribute to the placement of 20% to 30% of cases in one of the indeterminate BSRTC diagnoses (atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS], follicular neoplasm/suspicious for follicular neoplasm [FN/SFN], and suspicious for malignancy [SMC]). The remaining cases are placed in the benign (50%–70%), malignant (4%–8%), and unsatisfactory/nondiagnostic (10%–20%) categories. The demarcations between the categories are not always clear and are influenced by a variety of factors, including FNA sampling technique and yield, specimen processing, threshold for reporting cytologic atypia, interobserver variability in histopathologic interpretation of the resected nodule, tolerance of false-negative diagnoses, and methods used to calculate risk of malignancy.[4]

Some variability in practice is inevitable. Nonetheless, the BSRTC categories and subcategories (based on specific architectural and cytologic features) are associated with sets of differential diagnoses, depending on specific cytologic features identified (**Table 1**). For the benign diagnosis, the bland cytologic features of cellular elements usually ensure a benign outcome. However, some FNAs may sample focal areas of malignancies that, in part, are composed of deceptively bland-appearing neoplastic cells. In particular, large follicular variant papillary thyroid carcinoma (FVPTC) with macrofollicular areas and patchy distribution of diagnostic nuclear features may escape detection. Therefore, diagnostic scrutiny is warranted, especially for large nodules. The differential diagnosis for the AUS/FLUS diagnosis depends on the type of atypia identified: cytologic nuclear atypia (falling short of the "suspicious for malignancy" [SMC] diagnosis), architectural atypia (falling short of the "follicular neoplasm/suspicious for follicular neoplasm" [FN/SFN] diagnosis) or both. The FN/SFN cases are usually hypercellular specimens that do not show overt cytologic features of malignancy but are predominantly composed of microfollicles and/or syncytia; these cases reveal outcome possibilities including nodular hyperplasia, follicular adenoma (FA), follicular carcinoma (FC), FVPTC, and PTC with focal microfollicular pattern. Because the cytologic diagnosis of malignancy usually is based on nuclear details, the SMC and positive for malignancy (PMC) diagnoses share similar differential diagnoses. FC and cases of FVPTC in which the nuclear details are subtle would not be considered in the differential diagnosis of SMC or PMC.

Bethesda System for Reporting Thyroid Cytopathology diagnostic categories with cancer risk and recommended management

Category	Cancer Risk (%)	Recommended Management Based on Bethesda Guidelines
Unsatisfactory/Nondiagnostic	1–4	Repeat fine-needle aspiration (FNA)
Benign	0–3	Clinical follow-up
Atypia of undetermined significance/follicular lesion of undetermined significance	5–15 (for initial diagnosis) 20–25 (for repeat diagnosis)	Repeat FNA Consider lobectomy
Follicular neoplasm/suspicious for follicular neoplasm	15–30	Lobectomy
Suspicious for malignancy	60–77	Lobectomy or total thyroidectomy
Positive for malignancy	97–99	Total thyroidectomy

Data from Ali SZ. Thyroid cytopathology: Bethesda and beyond. Acta Cytol 2011;55:4–12.