Decision Making for Diagnosis and Management

Algorithms from Experts for Molecular Testing

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KEYWORDS

• Thyroid nodule • Thyroid cancer • Ultrasonography
• Fine-needle aspiration cytology • Biomarkers • Molecular classifier

KEY POINTS

- Assessment of risk of thyroid nodules requires understanding of clinical, demographic, imaging, cytopathologic, and now biomarker profiles; none of these factors alone represents a sufficient decision-making factor.
- Ultrasonography represents an accurate and cost-effective imaging modality for evaluating the thyroid, cervical lymphatics, and postoperative thyroid bed.
- Most solid or mixed thyroid nodules greater than 1 cm should undergo cytologic evaluation before surgery with increasing consideration for universal or selective use of biomarker assays.
- Biomarkers such as *Braf* add value to standard cytopathology in identifying suspected well-differentiated thyroid cancers.
- Biomarkers have prognostic value and with additional confirmatory information may help decision making regarding extent of surgical treatment and application of adjuvant treatments.

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INTRODUCTION

In 2013, in the United States, it was estimated that 60,220 new cases of thyroid cancer would be diagnosed and 1850 deaths would be caused by thyroid cancer.[1] Thyroid cancer affects women more often than men and usually occurs in people between the ages of 25 and 65 years.[2] The incidence of this malignancy has been increasing over the last decade.[2] Approximately 60,000 thyroid surgeries are performed annually, of which 33% (20,000) are thyroid lobectomies.[3]

Thyroid cancer risk factors include a history of radiation, goiter, a family history of thyroid disease, the female gender, and the Asian race.[4] Established clinical prognostic factors in well-differentiated thyroid cancer include age greater than 40 years, extrathyroidal/extracapsular invasion, vascular invasion, male gender, follicular disease, and tumors greater than 4 cm. Lymph node status does not seem to affect disease-free survival.

Risk of a nodule being malignant include size, cold nodule status, ultrasonographic (US) features (microcalcifications and increased nodular vascularity), a neck radiation exposure history, a family history in 1 or more first-degree relatives, associated lymphadenopathy on presentation, cytopathology (Bethesda grade) (**Box 1**, **Table 1**), and biomarker results (Afirma [Gene Expression Classifier Veracyte, Inc, San Francisco, CA, USA], MiRInform Thyroid [Asuragen, Inc, Austin, TX, USA], Thyroseq [University of Pittsburgh, Pittsburgh, PA, USA], microRNA).[5,6]

Molecular testing is a developing modality to be used judiciously in clinical practice. Much needs to be studied and reported regarding optimal and cost-effective use of molecular testing in the context of nodular thyroid disease (**Table 2**). This article includes cases that we hope show how molecular biomarker testing of thyroid nodule fine-needle aspirates (FNA) may be appropriately leveraged in a thyroid surgical practice (**Table 3**).

Box 1
The Bethesda system for reporting thyroid cytopathology: recommended diagnostic categories

I. Nondiagnostic or unsatisfactory
- Cyst fluid only
- Virtually acellular specimen
- Other (eg, obscuring blood, clotting artifact)

II. Benign
- Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule)
- Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
- Consistent with granulomatous (subacute) thyroiditis
- Other

III. Atypia of undetermined significance or follicular lesion of undetermined significance

IV. Follicular neoplasm or suspicious for a follicular neoplasm
- Specify if Hürthle cell (oncocytic) type

V. Suspicious for malignancy
- Suspicious for papillary carcinoma