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REVIEW

Role of ancillary testing in thyroid fine needle aspiration: Review and update

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Thyroid nodules are common, and ultrasound-guided fine needle aspiration identifies 70-75% as benign, and 4% as malignant. The remainder falls into categories of "indeterminate" with a widely ranging malignancy rate from 10-75%. The diagnosis and clinical management of indeterminate lesions is evolving, and we will review ancillary testing as an aid to diagnosis.

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Introduction

Thyroid nodules are common whereby palpation alone would identify nodules in approximately 5% of the US population. If ultrasonography is used, the prevalence of thyroid nodules would range from 20% to 70%.[1,2] Current guidelines classify cytologic interpretation into the following categories: non-diagnostic/unsatisfactory, benign, atypia of undetermined significance, suspicious for follicular/Hürthle cell neoplasm, suspicious for malignancy, and malignant.[3] Ultrasound-guided fine-needle aspiration identifies 70% to 75% of nodules as benign, and 4% as malignant.[3] The remaining 20% to 25% fall into the indeterminate categories of atypia of undetermined significance, suspicious for a follicular/Hürthle cell neoplasm, or suspicious for malignancy.[3] The malignancy risk for these indeterminate lesions varies from 10% to 75%.[3-6] Although morphology continues to solve the majority of cytological diagnoses, the increasing and accurate knowledge of the molecular mechanisms of cancer has opened to the application of ancillary techniques (both molecular and immunocytochemistry) on cytology with diagnostic and prognostic intents.[7-9] In fact, the clinical management of these indeterminate lesions is evolving, and there have been considerable efforts made to developing ancillary testing as a valid aid for the optimal management of these patients. Herein, we will review the various methods of ancillary testing in thyroid fine-needle aspiration and offer summary opinions of the future direction for this field.

Immunocytochemical markers

Immunohistochemistry has been part of the routine pathology practice since the beginning of the 1970s. First, it has been traditionally used on thyroid pathology for the identification of cell origin (such as thyroglobulin, calcitonin, or parathyroid hormone) in tumors arising either in the gland or outside it. Second, the introduction of the markers of malignancy, which may distinguish malignant from benign lesions irrespective the histologic features of carcinomatous evolution (especially capsular or vascular invasion), has represented a pillar of the morphologic diagnostics of thyroid cancer. In this latter perspective, numerous immunocytochemical (ICC) stains have been examined as potential markers of malignancy in thyroid fine-needle aspiration (FNA).[10,11] A significant challenge to this modality is the overlap in ICC marker expression between cases of indeterminate nodules and well-differentiated malignancies.[12,13]

HBME-1 (Hector Battifora mesothelial antigen) and galectin-3 have reached the highest specificity and sensitivity in discriminating between benign and malignant lesions mainly when used in panels.[11] Whereas HBME-1's epitope on the microvilli of the mesothelial is still unknown, galectin-3 is a well-characterized member of the family of beta-galactoside-binding lectins able to bind a cell surface as well as play a role in cell-cycle regulation and apoptosis.[14-16] As this protein up-regulates cellular interaction, an increase in expression may allow for tumor growth into adjacent tissues. There has been an association between galectin-3 and thyroid carcinoma, with a positive predictive value ranging from 78% to 100%.[16-18] Furthermore, it has been suggested that increased expression correlates with an aggressive clinical course, whereas the absence of this marker in carcinoma predicts a favorable course with fewer lymph node metastases.[14] Additional work has looked at the presence of galectin-3 as a method to determine which patients would benefit from surgical resection. A retrospective study estimated a 71% decrease in unnecessary surgeries; however, 6% of cancers would have been missed.[16,17] This brings into question the issue of what level of false-negative results are acceptable in an ancillary test used to determine candidates for surgical resection. An important point is the threshold used for making a positive interpretation has markedly varied from >10% of cells staining to >50%.[19] Also of note, there is no accepted standard methodology with regard to testing. Reports vary among the use of formalin-fixed paraffin-embedded material, conventional smears, or liquid-based preparations.[19,20] Nevertheless, it is essential to underline that none of the immunomarkers studied have shown a diagnostic accuracy sufficient for using them as single antibody characteristic of malignancy so that the use of an immunopanel made up of ≥2 immunomarkers is strongly encouraged by several investigators.[8,10,11,21-23]

Among the outstanding variety of markers studied and used to identify malignant lesions, a special note should be addressed in including HBME-1, cytokeratin 19 (CK19), and to a lesser extent CD44.[21,22] There are few published articles that highlighted the use of ICC in thyroid FNA cytology, including a series of 20 FNA cytology samples in which ICC was performed on cell-blocks yielding 100% sensitivity and specificity, and a recent article by Cochand-Priolet et al[23] who found identical results applying an ICC panel of HBME-1 and CK19 to 150 liquid-based cytology (LBC) thyroid specimens.[23,24] The results for indeterminate cytological cases favored malignant or benign disease with sensitivity, specificity, and negative and positive predictive values of 100%, 85.2%, 100%, and 86.2%, respectively.[23]

Some investigators have argued the specificity for a positive panel including HBME-1, CK19, and galectin-3 is such that lesions with this profile and indeterminate cytology may represent "preneoplastic" lesions.[25] In 2 different experiences, Fadda et al[26] and Rossi et al[27] highlighted the application of an ICC panel consisting of HBME-1 and galectin-3