Research Highlight

Preoperative diagnosis of benign thyroid nodules with intermediate cytology

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Thyroid nodules are very common and are diagnosed in over 7% of the adult population. However, most thyroid nodules are benign and only 5% harbor malignancy. Therefore it is of utter importance to develop safe and accurate tools that distinguish between benign nodules and malignant ones. At present, fine needle aspiration biopsy (FNAB) is considered the gold standard diagnostic tool for thyroid nodules. Despite a specificity of over 95%, indeterminate FNAB results are obtained in 15-30% of the cases. Indeterminate FNAB results include follicular lesions of unknown significance (FLUS), follicular lesions or neoplasms (FL or FN), and suspicious for malignancy. These specific FNAB results carry a malignancy risk of 5-15%, 15-30%, and 60-75% respectively (1). Such indeterminate FNAB results face both the patient and the surgeon with a treatment dilemma and in most cases patients undergo diagnostic surgery even though the majority of the cases turn out to be benign. The development of new and more accurate preoperative diagnostic techniques in such cases can eliminate the need of unnecessary diagnostic surgery. This article is a research highlight of the new and developing diagnostic techniques for such lesions.

Immunohistologic biomarkers lack the sensitivity & specificity to differentially characterize the FNA indeterminate cytopathologic subgroups of atypia/FLUS from FN or from suspicious for malignancy categories. Additionally, there is significant overlap of immunohistologic markers between cytopathologically indeterminate nodules and differentiated thyroid cancer (2).

The first method that demonstrated improved accuracy was ***testing for genetic alterations***. Papillary thyroid carcinomas contain BRAF and RAS point mutations, as well as RET/PTC and TRK rearrangements. These mutations are identified in up to 70% of papillary thyroid cancers (PTCs). About 70-75% of follicular thyroid cancers (FTCs) also carry mutually exclusive genetic alterations, namely, RAS point mutations or PAX8/PPARγ rearrangements. A recent meta-analysis revealed that out of 581 BRAF-positive thyroid FNAB samples, 580 (99.8%) were papillary carcinomas. Moreover, 15-39% of reported BRAF-positive FNAB samples were indeterminate or nondiagnostic on cytology, suggesting that BRAF also aids in the diagnosis of malignancy in nodules with indeterminate cytology. In FNAB samples, the detection of clonal RET/PTC is a strong indicator of papillary carcinoma, which is especially helpful for samples that are indeterminate on cytology or inadequate for cytologic evaluation (3). To assess the role of ancillary molecular studies in the diagnosis of thyroid lesions with "follicular lesion of undetermined significance/atypia of undermined significance" (FLUS/AUS) cytology, Ohori *et al.* evaluated 117 thyroid FNAB samples for BRAF and RAS mutations and RET/PTC and PAX8/PPARγ rearrangements. Molecular analysis and subsequent surgical resections demonstrated that the cancer probability for FLUS/AUS with molecular alteration was 100% while that without molecular alteration was 7.6%. These findings suggest that molecular testing of FNAB samples may refine FLUS/AUS cases into low- and high-risk categories, thereby increasing diagnostic accuracy (4).

More recently, numerous reports discussed the role of ***microRNA (miR) biomarkers*** in malignant thyroid cancer. miRs are short non coding RNA molecules that usually

function as negative regulators for the expression of protein encoding genes and are involved in cell development and apoptosis and may act as tumor suppressor genes or oncogenes. Dysregulation of different miRs have been described in various thyroid cancers including PTC, FTC, Medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC). miRs can characterize aberrantly activated metabolic pathways in malignant thyroid nodules. Protocols for miRs profile analysis are available for snap frozen tissues, formalin fixed paraffin embedded samples, and even cells obtained from FNAB (5). For miR analysis to be of diagnostic value, it should be extracted from cells obtained from FNAB. In a recent study using a panel of six miRs on a sample of 27 ex vivo FNAB, the accuracy for predicting PTC was 98% (6). Nevertheless, the accuracy for FTC is not as high and ranges between 70% and 90%. The added value of miR analysis in the evaluation of thyroid nodules with indeterminate FNAB results was also investigated with encouraging results that exceed the relatively low accuracy cytology results for these problematic scenarios. Yu *et al.* identified upregulated miRs in the serum of PTC patients and further demonstrated that levels decreased significantly after tumor excision (7). The diagnostic utility of miRs extracted from FNAB samples or from patients' serum is promising, however, it is limited by the high costs associated with the process.

One novel diagnostic technique that measures the expression of 167 genes has shown promise in improving preoperative risk assessment. A ***gene expression classifier (GEC)*** has been found to help identify nodules that are benign rather than malignant. The GEC uses the expression of 167 genes to classify nodules as either benign or suspicious. In a recent large prospective multicenter trial the GEC results were compared to histopathology of poperated nodules. The technique had a negative predictive value of 95% for aspirates classified as atypia of undetermined significance and 94% for aspirates classified as follicular neoplasms or suspicious for follicular neoplasms (8). This implied that thyroid nodules with these cytologic abnormalities and benign GEC results have a post test result probability of malignancy that is similar to the probability for nodules with cytologically benign features on FNA. The negative predictive value for aspirates with features of malignancy was lower (85%), and although the sensitivity was 100% for cytologically benign and cytologically malignant lesions, a specificity of 70% limits the use of the test in samples with benign cytologic features (8).

A unique technique of analysis is measurement of the ***Thyrotropin Receptor mRNA (TSHR mRNA)***. This technique measures the TSHR mRNA levels in the *blood* (derived from circulating thyroid cancer cells) and not on material obtained from a thyroid nodule by FNAB. This technology was combined with diagnostic thyroid ultrasonography and ultrasound guided FNAB and utilized to aid preoperative diagnosis of differentiated thyroid cancer. Eventually, the use of TSHR mRNA was reported for postoperative surveillance in follicular cell derived thyroid cancer to detect thyroid cancer persistence and recurrence. More recently, a large prospective study reported the validation of data for TSHR mRNA in both preoperative management of follicular neoplasms and the utility of the biomarker for thyroid cancer surveillance. It was found that when used in combination with diagnostic ultrasound and a FNAB result of follicular neoplasm, it has a sensitivity of 97% and specificity of 88% for predicting thyroid cancer (9).

To summarize, the preoperative evaluation of a thyroid nodule still relies on FNAB and indeterminate FNAB cytology results pose a diagnostic and management challenge. Diagnostic surgery is most commonly performed for such indeterminate results and turns out to be unnecessary in the majority of the cases. However, the above mentioned technologies and techniques seem to be promising and may very well replace diagnostic surgery in the near future.

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