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Review Article

Types and role of cytological molecular analysis in thyroid carcinomas

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ABSTRACT

Estimates show that thyroid nodules are commonly reported among populations residing in iodine-sufficient countries, with estimated prevalence rates of 1%, and 4% of palpable nodules among men and women in these countries, respectively. Furthermore, early diagnosis can effectively direct clinicians to the right management modality, especially in cases with malignant lesions. In this literature review, we have discussed the types and roles of cytological molecular analysis in thyroid carcinomas. Our findings indicate the molecular analysis can significantly add to the diagnostic accuracy of cytological analysis and can greatly add to the efficacy of differentiating benign from malignant lesions. We have discussed the roles of different genetic mutations that were reported among the various studies in the literature, including BRAF, RAS, PAX8/PPARγ, and RET mutations. BRAF mutations are the most validated mutations among the current studies in the literature, which has been reported to greatly increase the positive predictive values in detecting thyroid carcinomas. Some genetic mutations can be used to diagnose difficult to differentiate malignancies by fine needle aspiration (FNA) analysis. For instance, RAS mutations were reported to accurately diagnose follicular variants of papillary thyroid carcinomas that are difficult to detect using routine FNA analysis.

Keywords: FNAC, Genetic mutations, Molecular analysis, Thyroid carcinomas

INTRODUCTION

Estimates show that thyroid nodules are commonly reported among populations residing in iodine-sufficient countries, with estimated prevalence rates of 1%, and 4% of palpable nodules among men and women in these countries, respectively. However, it has been estimated that only 19-67% of these cases can be detected by ultrasound.[1] Besides, an estimated rate of 5-15% of the thyroid nodules is attributable to malignant lesions, which were also reported to significantly depend on age, sex, family history, radiation exposure, and other factors.[2] Early diagnosis can effectively direct clinicians to the right management modality, especially in cases with malignant lesions.[3] Accordingly, many diagnostic approaches have been proposed to enhance the diagnosis and adequately differentiate benign from malignant lesions.

Evidence shows that conducting fine needle aspiration (FNA) analysis has been considered the most reliable and valid approach to diagnose thyroid nodules and has also been reported to effectively differentiate between malignant and benign lesions in most cases. However, it should be noted that in 10-40% of the cases that have been approached with FNA analysis, indeterminate malignancy diagnosis would be established.[4-6] Many categories have been reported under the word indeterminate malignancy by FNA analysis, including follicular or Hürthle cell neoplasm/suspicious for follicular or Hürthle cell neoplasm (FN/SFN), atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), and suspicious for malignancy (SFM). Estimates show that all of these subcategories might correlate for the diagnosis of malignancy at a rate of 20-30%, 5-10%, and 50-75%, respectively.[7] Figure 1 summarizes the molecular pathways and pathogenesis of thyroid cancers.

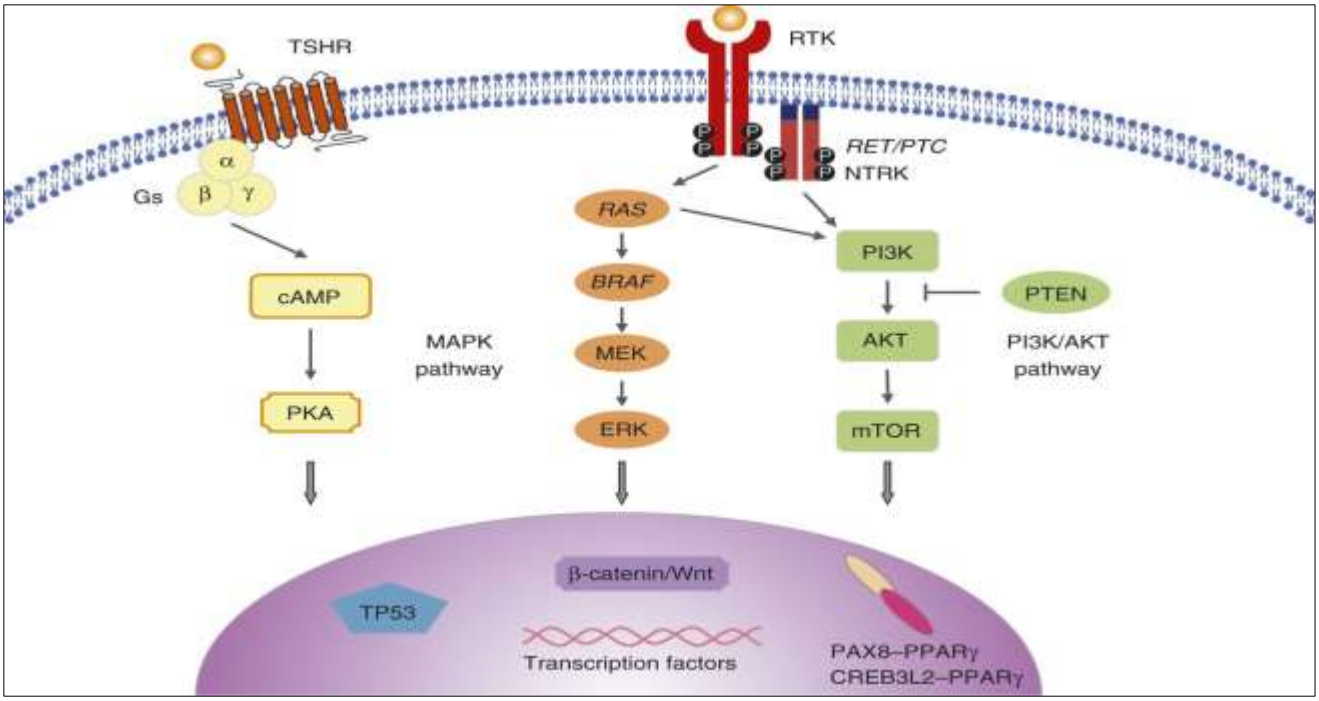

Figure 1: The molecular pathways and pathogenesis of thyroid cancers.[8]

Furthermore, many cases with thyroid nodules usually undergo surgery for removal of the nodules as a result of the non-specific diagnosis and inability to differentiate benign from malignant cases. However, it has been demonstrated that only around 8-17% of the thyroid nodules that were surgically removed are malignant.[9] Moreover, evidence also shows that that patients with indeterminate cytological analysis or malignant lesions are usually not adequately managed. This usually happens because most of these patients are usually initially indicated for thyroid lobectomy that is also often followed by thyroidectomy. Accordingly, it was essential to provide more reliable modalities that can differentiate benign from malignant lesions and establish a proper diagnosis. Molecular analysis for the obtained samples has been validated as a significant modality with many favorable outcomes. It has been demonstrated that testing for mutations (by RAS, BRAF, PAX8/PPARγ, and RET/PTC) has been associated with a significant increase in the specificity, however, no major enhancements were noticed in terms of sensitivity.[10] We, hereby, aim to discuss the role of cytological molecular analysis in thyroid carcinomas based on the current evidence from studies in the literature.

METHODS

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 20 August 2021 using the medical subject headings (MeSH) or a combination of all possible related terms. Papers discussing the role of cytological molecular analysis in thyroid carcinomas were screened for relevant information, with no limitation on date, language, age of participants, or publication type.

DISCUSSION

FNA biopsies can be used to detect RAS, BRAF, PAX8/PPARγ, and RET/PTC mutations by molecular analysis to adequately diagnose a malignant lesion, if present. This can aid in the accuracy and specificity of the FNA cytology tests. Besides, previous studies have demonstrated that in cases of indeterminate cytology, molecular analysis for genetic and protein markers can significantly enhance the diagnostic accuracy before performing a surgical procedure.[11,12] In this context, the 2009 revised american thyroid association (ATA) management guidelines for patients with thyroid nodules

and differentiated thyroid cancer has recommended the use of molecular testing for detection of molecular markers and adequately establish a valid diagnosis.[1] Regarding BRAF V600E, many studies have demonstrated its efficacy in enhancing the diagnostic accuracy of FNA cytological analysis.[11,13-15] This has been indicated in a meta-analysis by Nikiforov that showed that among the 581 cases with thyroid nodules that were BRAF-positive, 580 cases were papillary thyroid carcinomas.[16] This indicates the huge diagnostic efficacy of the modality in detecting thyroid malignancy. In the same context, previous studies have also demonstrated that around 15-39% of the BRAF-positive samples were indeterminate by FNA cytological analysis. Therefore, the significance of molecular analysis for BRAF positivity has been indicated in establishing a proper diagnosis.[12-14,16] Zatelli et al also concluded that BRAF-positivity helps to establish a diagnosis of the FNA-cytology indeterminate cases, however, it should be used as a complementary modality to ultrasound and cytology.[17] Moreover, previous studies have demonstrated that BRAF V600E was associated with malignant ultrasound characteristics, including irregular margins, significant hypoechogenicity, solid composition, the presence of calcifications, and taller than wider shapes, in addition to predicting increased tumor size and poor prognostic factors.[18,19]

In another context, it has been reported that detection of BRAF is of limited importance in the diagnosis of follicular thyroid carcinomas.[20] However, it was demonstrated that molecular analysis can help detect metastasis following the surgery. Furthermore, another investigation aimed to evaluate the value that BRAF detection can add to the diagnostic ability of FNA analysis with and without ultrasound guidance. The authors reported that cytological analysis had good specificity and positive predictive values, and BRAF was positive in 115 samples, of whom 80 cases were found to be papillary thyroid carcinomas. Therefore, it has been concluded that BRAF detection can enhance the diagnostic efficacy of cytological analysis, and a rate of 28% has been estimated for enhanced sensitivity of the diagnostic modality.[21] Another investigation by Howell et al also retrospectively evaluated patients that were indicated for thyroidectomy as a result of papillary thyroid carcinomas.[22] The authors evaluated the association between different preoperative demographic and clinical parameters including age, sex, BRAF positivity, and tumor size, and the presence of central compartment lymph node metastasis (CLNM). The analysis results of this study showed that only BRAF V600E was the only predictor for the presence of CLNM in patients with papillary thyroid carcinomas. Therefore, it has been concluded that BRAF can significantly be used for the follow-up of post-surgery status.[22] Another investigation by Kabaker et al also showed that BRAF positivity was an indicator for several suspicious lesions on ultrasound, including poorly-defined margins, hypoechogenicity, calcifications, taller than wider shapes, and halo absence.[23] Accordingly, it has been estimated that the negative predictive value, when no ultrasound characteristics were detected BRAF was negative, was 88%, while the positive predictive value was estimated to be 82% when 2-3 features were detected on ultrasound, and BRAF was positive. The efficacy of BRAF has been furtherly validated by more recent studies, which showed that the estimated positive predictive value was 99.9%, and the estimated specificity was 97.9%, with a minimal number of false-positive cases.[24-27] The previous review by Rodrigues et al has evaluated the different techniques that can be used to detect BRAF and other markers.[28]

Molecular testing of the RET/PTC rearrangements can also help with the diagnosis and differentiation of thyroid nodules. Studies showed that the modality can aid in the diagnostic accuracy of FNA cytology, especially in cases when the cells are not adequate within the sample to establish a diagnosis, or when there is an indeterminate diagnosis of thyroid nodules.[13,14,29] Previous two prospective investigations have indicated that all of their included samples of papillary thyroid carcinomas, that were determined by FNA cytology, were all positive for RET/PTC analysis.[12,30] In another investigation, 5 out of 6 samples that were positive for RET/PTC rearrangements were found to be malignant, and only 1 positive sample had benign characteristics.[11] Accordingly, it has been concluded that RET/PTC can significantly help with the diagnosis and differentiation of thyroid nodules. Ferraz et al indicated that RET/PTC can be associated with better diagnostic outcomes than the outcomes that can be obtained with FNA cytology alone.[31] Another meta-analysis by Rodrigues et al estimated that the specificity and positive predictive value for RET/PTC positivity in establishing a proper diagnosis of thyroid nodules were 18%, and 87%, respectively.[28] It has been demonstrated that the diagnosis of the follicular variant of papillary thyroid carcinoma is difficult, especially with FNA cytology. However, it has been demonstrated that the molecular detection of RAS mutations can significantly help with the diagnosis process of this malignancy. Gupta et al reported that RAS mutations are the second commonest types of mutations that can be detected using FNA cytological analysis, and might result in the development of thyroid nodules.[32] In a previous retrospective investigation that recruited 341 patients with thyroid malignancies, Mehta et al reported that the diagnosis of malignancy in these patients was significantly associated with N-RAS mutations, the findings, of FNA cytology analysis, and the presence of tissue inhibitor of metalloproteinases-1.[33] Studies have estimated that the positive predictive values for malignancies were 74% and 88%.[12,30] Detection of RAS mutations could significantly enhance the ability to detect tumors that were difficult to diagnose with FNA cytology. These malignancies include follicular variants of papillary thyroid carcinoma and follicular thyroid carcinomas. However, studies have also demonstrated that false-positive results might also be present with RAS mutations, indicating the presence of benign follicular adenomas. It has been suggested that the detection of such events might predispose to the development of malignant lesions. Besides, it has been

demonstrated that RAS positivity might help with the process of classification and grading of tumors.[34,35]

The meta-analysis by Rodrigues et al estimated that the specificity and positive predictive value for RAS positivity in establishing a proper diagnosis of thyroid nodules were 23%, and 82%, respectively.[28]

Positivity for PAX8/PPARγ rearrangements does not necessarily lead to a diagnosis of malignancy. However, it has been reported that can predict capsular and vascular invasions. Therefore, might help with the grading process. Studies have demonstrated that such lesions are not usually observed at first. Nevertheless, conducting an adequate examination of the whole capsule would establish a proper diagnosis and indicate the invasion in cases with PAX8/PPARγ positivity.[36,37] Besides, previous prospective studies have shown that PAX8/PPARγ can be positive in some FNA samples, indicating its ability to detect malignancy. However, these samples are few, and further studies for adequate validation are needed.[12,38] This was also indicated in the study by Ferraz et al.[31] Moreover, the meta-analysis by Rodrigues et al estimated that the specificity and positive predictive value for PAX8/PPARγ positivity in establishing a proper diagnosis of thyroid nodules were 20%, and 100%, respectively.[28] Detection of multiple mutations was also validated by some previous investigations, which indicated that it might have superior accuracy over FNA cytology and over detecting single mutations. This has been indicated in a previous prospective investigation, which showed that the estimated sensitivity of FNA alone or in combination with multiple genetic mutations including BRAF, RAS, RET/PTC, and PAX8/PPARγ was 44%, and 80%, respectively.[12] The same study also showed that most of the cases (97%) that were positive for genetic mutations were malignant, and only one that was positive for RAS mutations was composed of benign follicular nodules, following the surgery.[12] Therefore, it has been concluded that the detection of genetic mutations can significantly help with establishing a proper diagnosis of thyroid cancer. The authors also indicated that detecting genetic mutations helped with the diagnosis of malignancy in 71% of the cases that were indeterminate with FNA analysis. Another investigation indicated that the sensitivity of FNA cytology increased from 60% to 90% when the modality was combined with detecting genetic mutations of TRK, RET, PAX8/PPARγ, RAS, and BRAF.[30] On the other hand, a previous investigation by Borrelli et al indicated that detecting BRAF mutations did not significantly enhance the diagnostic accuracy of cytology.[39] The authors reported that BRAF mutations were only detected in 4.4% of the included patients with indeterminate cytological analysis using the easy BRAF kit. Studies have also detected genes within BRAF-mutated papillary thyroid carcinomas that are not usually detected in wild-type tumors. Furthermore, these genes include cadherin-associated protein (catenin), α1, 102 kDa (CTNNA1), TIMP metallopeptidase inhibitor 1, fibronectin 1 (FN1), and secreted phosphoprotein 1, which were upregulated, in addition to other two genes, including SELL, and ADAMTS1, which were downregulated. Other six genes were also found to be upregulated in malignant versus benign lesions, including transforming growth factor, β-induced, collagen, type I, α1, CTNNA1, FN1, cadherin 1, type 1, and integrin α3. Other six genes were also found to be upregulated in follicular variant papillary thyroid carcinomas as compared to thyroid follicular adenomas. These include connective tissue growth factor, FN1, integrin β2, laminin γ1, integrin αV, and cadherin-associated protein (catenin), δ1.[40-42]

CONCLUSION

Molecular analysis can significantly add to the diagnostic accuracy of cytological analysis and can greatly add to the efficacy of differentiating benign from malignant lesions. BRAF mutations are the most validated mutations among the current studies in the literature, which has been reported to greatly increase the positive predictive values in detecting thyroid carcinomas. Some genetic mutations can be used to diagnose difficult to differentiate malignancies by FNA analysis. For instance, RAS mutations were reported to accurately diagnose follicular variants of papillary thyroid carcinomas that are difficult to detect using routine FNA analysis.

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