MIRNA EXPRESSION ANALYSIS COMBINED WITH THE DETECTION OF ACTIONABLE GENETIC ALTERATIONS IMPROVES THE DIAGNOSTIC SENSITIVITY OF MOLECULAR CYTOLOGY IN PREOPERATIVE THYROID NODULE ASPIRATES

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Background: One of the objectives of molecular testing during the preoperative evaluation of thyroid nodules with inconclusive cytology is to accurately diagnose patients with cancer who could benefit from initial total thyroidectomy rather than diagnostic lobectomy followed by completion thyroidectomy. This goal can be achieved through the specific detection of genetic alterations commonly found in thyroid cancer. However, up to 40% of malignant specimens do not carry any of the common founding mutations. In this study, we set out to establish a miRNA signature specific for thyroid carcinoma and assessed its performance in combination with a panel of well-established oncogenic gene mutations.
Methods: Formalin-fixed, paraffin-embedded (FFPE) specimens from diverse benign and malignant thyroid lesions were used to evaluate 31 miRNA candidates by quantitative RT-PCR using microRNA LNA PCR primer sets (Exiqon). A classifier was developed by Diagonal Linear Discriminant Analysis and cross-validated in a subset of benign and malignant lesions. The miRNA signature was then evaluated in a broader set of FFPE specimens (n=247) and in thyroid nodule fine needle aspirates (FNAs) (n=100). All specimens were also analyzed for the presence of 17 distinct oncogenic gene alterations using the miR*Inform*™ Thyroid testing service (Asuragen).
Results: Quantitative analysis of 5 miRNA in well-characterized FFPE specimens resulted in cancer detection rates of 16 to 100% among various thyroid carcinomas (follicular, anaplastic, poorly differentiated and papillary classical, tall cell or follicular variants). All benign cases and 89% of the follicular adenomas were negative. A genetic alteration in the BRAF, HRAS, KRAS, NRAS, PAX8 or RET genes was detected in 27 to 90% of the various thyroid carcinomas and 46% of the mutation-negative specimens were positive by miRNA expression analysis. Evaluation of preoperative FNAs showed that 50% of the mutation-negative malignant cases could also be similarly identified by the miRNA classifier.
Conclusions: We have developed a 5-miRNA classifier that can improve thyroid cancer detection rates in nodules negative for oncogenic mutations and may further advance the personalized management of thyroid cancer patients. Additional validations studies in preoperative FNAs with indeterminate or non-diagnostic cytology are ongoing and will be reported.