Abstract

Thyroid nodules are rare in pediatric and adolescent patients, but they are at greater risk of malignancy than adult patients. Thyroid carcinomas are the most common endocrine malignancy and their incidence is increasing. Although there are several types of thyroid carcinoma, 90% of cases in pediatric and adolescent patients are papillary thyroid carcinomas (PTCs). The aim of this study was to analyze a large cohort of PTCs from pediatric and adolescent patients, determine their genetic cause, and correlate the findings with clinical pathological data. Another aim was to characterize the most frequent findings and compare them with a cohort of adult patients with thyroid carcinoma positive for the same mutation. The final objective was to optimize a suitable methodology for detecting the most common findings in pediatric and adolescent patients for routine use.

Thyroid tumor tissue samples were examined using molecular genetic methods, mostly using next-generation sequencing and real-time PCR analysis. We found that fusion genes were the most common cause of PTC in pediatric and adolescent patients, detected in 56% of patients. In total, 20 different types of fusion genes were identified, some of which have not been previously described in the literature. The fusion genes included the oncogenes *RET*, *NTRK*, *BRAF*, *ALK*, *MET*. Other genetic alterations were point mutations in the *BRAF* and *RAS* genes. Overall, we were able to identify the genetic cause in 77% of patients. When comparing PTCs positive and negative for the fusion gene, we found that PTCs positive for the fusion gene were more aggressive and patients underwent more intensive treatment. The most common findings were *RET* and *NTRK* fusion genes, which we also analyzed in the adult cohort. We characterized the positive findings based on common features. We also performed comparisons between cohorts of pediatric and adult patients with the same type of mutation (*RET* or *NTRK* fusion gene). Based on our results, we established a method for detecting fusion genes in both preoperative and postoperative thyroid specimens, which has proven successful in routine practice.

This dissertation is a significant contribution to the understanding of the pathogenesis of PTC in pediatric and adolescent patients and, in addition, the results of this work are applicable in routine practice.

Key words: papillary thyroid carcinoma, children and adolescents, gene, mutation, fusion gene, *RET*, *NTRK*