



**GEORGE EMIL PALADE UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY
FROM TÂRGU MUREȘ - DOCTORAL STUDIES MEDICINE AND PHARMACY**

Summary of the doctoral thesis:

**Morphological, immunohistochemical and molecular study to identify factors with a role in
stratifying the risk of aggression in papillary thyroid carcinomas**

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Worldwide, the incidence of papillary thyroid carcinoma (PTC) has significantly increased over recent decades. This is mainly related to the rapid increase in the incidence of small, incidentally discovered, subcentimetric papillary thyroid carcinomas, namely microcarcinomas (PTMC). PTMC becomes a more and more frequent diagnosis in many countries around the world. It is accepted that these small papillary thyroid cancers are common and rarely behave as aggressive cancers, with extrathyroidal extension and lymph node and distant metastasis. Therefore, the biological characteristics of PTMC have gradually attracted more attention from researchers. The main questions for the clinician remain (1) how to distinguish between harmless and harmful PTMCs and (2) which PTMCs can adequately and safely be managed by active surveillance as an alternative to immediate surgery.

This thesis brings valuable information about PTMCs, tumors responsible for a phenomenon referred to as thyroid cancer “overdiagnosis” or as an “epidemic of diagnosis”. The first study aimed to analyze and assess the morphological features of PTMCs in a large series of cases, including <5mm and ≥5mm tumors. Our aim was to determine whether small (<5mm) tumors by contrast with large (≥5mm) ones are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness and could thus be regarded as low-risk cancers. In conclusion, we demonstrated that small (<5mm) PTMCs are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness compared with large (≥5mm) tumors.





In this context, the second study was born, which aimed to determine in our series of cases whether two clinically accessible parameters, tumor size and location within the thyroid, correlate with clinico-pathological features that are predictors of high risk in PTMCs and consequently whether they could have an impact on the clinical management of patients with PTMC. We demonstrated, by evaluating the two important clinically accessible morphological parameters (tumor size and location), that correlate with specific clinicopathological factors, enabling easy four-group risk subdivision of PTMC cases. This subdivision of PTMCs could have a clinical impact on the preoperative assessment of subcentimeter thyroid nodules. Our results have shown that a closer, more attentive follow-up and management is justified for large (≥ 5 mm) subcapsular tumors, since they seem to be associated with high-grade morphological features. By contrast, most other PTMCs, and in particular those that are small (< 5 mm) and non-subcapsular, may be considered appropriate candidates for active surveillance programs. However, further larger studies with long-term follow-up data are needed to confirm these results.

In the third study we performed a molecular and immunohistochemical study to validate the immunohistochemical technique in detecting the BRAF^{V600E} mutation by comparison with the molecular techniques, PCR technique, considered as reference (gold standard). We demonstrated that immunohistochemistry has a good concordance compared to the PCR technique in detecting the BRAF^{V600E} mutation in PTC cases. Immunohistochemistry is a feasible and easily reproducible method. Although in small numbers, the existence of false positive and false negative cases in our study group (similar to the data in the literature) draws attention to the fact that, where there is a high suspicion for the presence of BRAF^{V600E} mutation based on morphological criteria (certain histological variants, extrathyroid extension, lymph node metastases) and one of the two methods is negative, it would be ideal to supplement with the second.

