



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

Summary of the doctoral thesis with the following title:

***Thyroid carcinoma originating from follicular cells: epidemiology, morphology and
molecular biology studies for identifying factors with potential impact on clinical
management***

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Thyroid carcinoma originating from the follicular cells represent the most frequent form of endocrine carcinoma. In the past decades, an ascending trend in their incidence rate has been recorded. Taking into consideration the spectacular evolution of the classification of the thyroid carcinoma between 1950 and 2017, an understanding of the history, cause and clinical impact of these changes, along with a clarification of the molecular mechanisms of the thyroid carcinogenesis, are both essential for a correct diagnosis and management of these patients. In this context, our research puts forward a multidisciplinary approach of this subject from various perspectives – an absolutely necessary endeavor for a more accurate classification of thyroid carcinoma and for the opportunity to implement individualized therapy.

The first study focuses on the Mureș county and the surrounding areas over the past 26 years, providing valuable information on the epidemiology and the evolutionary trend in the histopathology of the carcinomas originating from the follicular cells. In our institution, the occurrence rate of the carcinomas originating from the follicular cells followed an upward trend over the past three decades. The increase is directly proportional to the number of surgical interventions, which can be caused by an improved access to healthcare, as well as an increasingly frequent use of medical imaging for establishing a diagnosis. The trend in histopathology has suffered significant alteration, being dominated by a prominent increase in the incidence rates of follicular thyroid carcinoma and papillary thyroid microcarcinoma, a phenomenon named epidemic of overdiagnosis.

Taking into consideration the abovementioned ascending trend in the incidence rate, a re-evaluation of the morphological characteristics in the diagnosis and the management of well-differentiated thyroid carcinomas originating from the follicular

cells was necessary. This has been conducted in the second study. The current classification of thyroid tumors reflected in the 2017 World Health Organization Classification of Tumors, as well as the 2016 8th (and latest) edition of TNM staging system for thyroid cancer have both introduced significant changes in the histopathological criteria of diagnosing and staging thyroid carcinoma. After having applied the recent 2016 TNM criteria to our study, there has been a favorable restaging (stage I or II) in a significant percentage of patients, with an observable 53% downstaging rate. This rate is caused on one hand by the new classification of the noninvasive follicular thyroid neoplasm – formerly known as encapsulated follicular variant of papillary thyroid carcinoma – and on the other hand by the modification in the definition of the extrathyroidal extension and the age cutoff in staging thyroid carcinoma. These results prove that, in the past, some of the patients received more aggressive treatment than necessary, with higher costs and significant physical and psychological impact. To our knowledge, no other research study has approached this issue to date, therefore underlining one of the original aspects of the current paper.

For a better classification and characterization of the thyroid lesions' carcinogenesis, we conducted a molecular biology study by means of which we evaluated the molecular profile of thyroid carcinoma originating from follicular cells. The results prove the distinct clinical, morphological and evolutionary profiles of the *BRAF*-like versus *RAS*-like tumors. Therefore, in contrast with patients with *RAS*-positive tumors, the ones with *BRAF*^{V600E}-positive thyroid carcinoma were of older age at the moment of diagnosis. In addition, the ones from the latter group were also predominantly male and presented a significantly higher rate in multifocality, extrathyroidal extension and lymph nodular metastasis. After five years without the occurrence of adverse events, the survival rate of the aforementioned patients was significantly lower comparatively to the survival rate of the group with *RAS* mutation. The results underline the indolent characteristic of these tumors. The obtained correlations demonstrate the prognosis role of the *BRAF*^{V600E} mutation in the occurrence of adverse events (persistent/recurrent disease) in the case of papillary thyroid carcinoma.

Another original aspect of the present paper is the last study, which consists of the translation and validation of an instrument for measuring the quality of life in patients with thyroid disease. *ThyPROro* is the first validated questionnaire that can be applied to Romanian patients with thyroid disorders. The study of the quality of life in patients with thyroid disease is an ongoing matter, extremely necessary in the standard practice.

All in all, we consider that by means of these studies we have succeeded in our efforts to gather valuable results regarding thyroid carcinoma originating from the follicular cells that can significantly impact the management of individualized therapy and can be applied in day-to-day medical practice.