

UNIVERSITY OF MEDICINE AND PHARMACY TÎRGU- MUREȘ
SCHOOL OF DOCTORAL STUDIES

THE MANAGEMENT OF THYROID NODULES

-abstract-

PhD student: Ramona Teodora Cătană

Scientific Coordinator: Prof. Univ.Dr. Angela Borda

Thyroid nodular disease is one of the most common endocrine disorders encountered in the current medical practice, with a prevalence estimated by ultrasonography reaching up to 76% in the general population. Thyroid nodules are the clinical expression of a broad spectrum of thyroid disorders. For an accurate selection of the patients at increased thyroid malignancy risk, several management guidelines have been developed lately. However, the final diagnosis of certainty is established by the histopathological examination in standard hematoxylin-eosin staining. Many times the pathologist faces real difficulties in classification of the thyroid follicular lesions. In order to improve this diagnosis, it has been proposed the use of various immunohistochemical markers, with discordant results yet.

The thesis is structured in two main parts. The **general part** of the thesis presents a review of the literature data regarding the epidemiology, pathogenesis and pathology of thyroid nodules. Investigating aspects of the patients with this pathology and diagnostics particularities of tumors with follicular architecture are also presented, highlighting the role of immunohistochemistry in these cases.

The **experimental part** is structured in three distinct parts:

1. Epidemiological and pathological aspects of the nodular thyroid pathology in the last 23 years in Mureș county and area

The aim of the study was to investigate time trends of thyroid pathology and to analyze the distribution of the different histological forms.

Material and methods: the study is a retrospective review of thyroid pathology (1990-2012), in Mureș County. All patients who underwent a total or partial thyroidectomy in the Surgery Department I and II of Tîrgu-Mureș Emergency County Hospital and whose surgical thyroid specimens had nodules were included.

Results: from the 3935 patients (M/W: 1/8,3), 3177 (80.73%) had benign nodular lesions, and 758 (19.27%) malignant tumors;

Malignant nodules had a mean frequency of 10% before 2000 and recorded an increasing trend in the second half of the period, representing in 2010, 30% of all thyroid nodules. Papillary carcinoma (CPT) is the most frequent malignant histology (83%). In the recent years (2009-2010), the incidence of the follicular variant of CPT exceeded the incidence of the conventional form, the predominant form until then.

Thyroid microcarcinomas (tumors ≤1cm in size) represented 26.78% of all malignant tumors (203 cases), 99% of them being CPT. A statistically significant increase in its incidence was recorded between 2001-2012 (194 cases- 29.7%) compared to 1990-2000 (9 cases- 8.57%), (p=0.0001).

Conclusions: Our study demonstrated increasing trends in the incidence of thyroid cancer in the last 23 years. This increasing trend seems mainly due to a rise in incidence of the papillary type, often small sized (<1cm), accidentally diagnosed after a detailed examination of the specimens. A better understanding and description of the morphological criteria, according to which the gold standard diagnostic is nuclear criteria rather than the architecture, could explained the increasing incidence of the follicular variant of CPT.

2. Correlative analysis of some anamnestic, clinical and laboratory aspects with the histopathology of the thyroid nodules

The **aim** of the study was to evaluate the possibility of an accurate diagnostic classification of thyroid nodules in the categories benign/malignant, based on anamnesis, clinical and laboratory examinations.

Material and methods: we performed a prospective analysis between September 2009-October 2010 in Surgery Department I and II of Tîrgu-Mureş Emergency County Hospital, which included the patients diagnosed with thyroid nodules. Face-to-face interviews were conducted to obtain a complete medical history and to register laboratory, imaging and cytology results.

Results: the study included 164 patients (M /W: 1/8.64, mean age: 50 years). Among patients who reported the presence of cervical symptoms, most accused choking sensation (75.92%-78.43%). The highest frequency of malignancy was recorded in patients disturbed by the occurrence of a cervical lump, but without symptoms (44%). Menstrual and obstetrical antecedents have not been associated to a higher risk of thyroid cancer. Although, there was a discrete increase of malignancy rate, in obese patients and those presenting TSH values in the second half of the reference range, these associations are not significant. At ultrasound examination malignant nodules are more frequently solid (76.7% vs. 53.9%) and hypoechogenic (53.4% vs. 44.1%). In order to diagnose the malignant nodules, fine-needle aspiration (FNA) obtained a sensitivity of 52% and 100% specificity.

Conclusions: In most of the cases, the cervical symptoms cannot be related to the presence or the size of thyroid nodules. Our study indicates a slightly higher frequency of malignant tumors among obese patients. The study suggests the susceptibility to thyroid malignancy with increasing TSH value, recognized as a major factor for follicular cell proliferation. FNA contributes to reducing unnecessary thyroid surgeries. The ultrasound examination requires the constancy of the physician-device couple.

3. The importance of immunohistochemical markers in the diagnosis of nodular thyroid lesions

The **aim** was to evaluate the diagnostic value of four antibodies (HBME-1, Galectin-3, CK19, CD56) and their possible combinations in series of benign and malignant thyroid lesions and to investigate their importance in diagnosis of the thyroid tumors of uncertain malignant potential (TT-UMP).

Material and methods: We performed an immunohistochemical analysis in the Department of Histology of Tîrgu-Mureş University of Medicine and Pharmacy, using TMA (tissue microarray analysis) technique. The study included 11 benign lesions (5 follicular adenomas, 3 nodular goiters, 3 chronic lymphocytic thyroiditis), 11 CPT (6 conventional variants CVCPT, 5 follicular variants FVCPT) and 31 thyroid tumors of uncertain malignant potential (TT-UMP).

Results: CD56- considered negative test for malignancy- had the highest sensitivity (Se-81.81%) in differentiating malignant from the benign nodules and 63.63% specificity (Sp). Gal3 and CK19 were negative markers for the benign lesions and for the FVCPT cases, obtaining 100% specificity, but low sensitivity 45%. HBME-1 was positive in 27% of benign lesions and in 63% of malignant tumors (Se 63.63%; Sp72.72%). The association of CD56 with either Gal3 or CK19 had the best sensitivity (90.9%) with 63.63% specificity. The panel of HBME-1 with either Gal3 or CK19 gets a better specificity (72.72%) but lower sensitivity (81.81%). The results of TT-UMP immunohistochemical reactions are similar to those obtained by the benign lesions.

Conclusions: There isn't a perfect immunohistochemical antibody or panel of antibodies in differentiating thyroid nodules, but the most useful appears to be CD56, surpassing the performances of HBME-1. CD56 sensitivity can be enhanced by panel association with CK19 or Gal3. Used individually CK19 or Gal3 have no value in the differential diagnosis of VFCPT vs. benign follicular lesions. TT-UMP demonstrated a benign immunohistochemical profile. Our results could be of particular interest as a complement to the morphological criteria in the difficult cases of follicular thyroid lesions.

Keywords: thyroid nodules, thyroid cancer, symptoms, obesity, TSH, FNA, immunohistochemistry, CD56, HBME-1.