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Abstract of the Ph.D. thesis:

Morphological, immunohistochemical and molecular aspects of gastric and colorectal carcinomas

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Colorectal carcinomas (CRC) and gastric carcinomas (GC) still present an increasing incidence and are an important cause of cancer-related death. Their genesis and progression are determined by a combination of genetic and environmental factors that need to be studied in order to determine new prevention strategies. The discovery and use of new sensitive and specific biomarkers may enable the diagnosis of these carcinomas in their early stages, respectively the individualized treatment.

This paper includes complex studies that aimed to identify the prognostic differences and those related to the molecular profile of gastrointestinal carcinomas, from the perspective of molecular events from the tumor center versus the invasion front/tumor buds. The studies enabled the identification of those immunohistochemical (IHC) markers useful to be included in the guidelines for the diagnosis and transdisciplinary therapy of gastrointestinal carcinomas.

In the case of CRC, we redefined the tumor buds, recognized as a prognostic factor, by carefully examining the cell expression of Maspin, in the tumor center versus the invasion front. Based on the obtained results, their correlation with the clinicopathological parameters and the overall survival rate (OS), we tried to establish a protocol for quantifying the buds, easy to use in daily practice and with prognostic importance.

In order to examine the molecular profile of CRC, we focused on a less-understood mechanism of tumor invasiveness and metastasis, namely epithelial-mesenchymal transition (EMT). The working hypothesis was the possible involvement of Maspin in the EMT process of the tumor cells. We also assumed that EMT could be a useful parameter for

the molecular classification of CRC, performed for prognostic purposes, classification based on IHC reactions. The obtained correlations aided the molecular subtyping of the CRC in the epithelial, mesenchymal and hybrid subtypes, easily identifiable in daily practice and with possible prognostic and/or predictive importance.

In the case of primary GC, we tried the intraoperative and postoperative mapping of sentinel lymph nodes (SLN), using the methylene blue dye, in order to identify the "aberrant" lymph node metastases (skip metastases). We mainly pursued the practical importance of the method used, namely the standardization of the multidisciplinary examination method of SLN, from intraoperative sampling to histopathological examination and identification of micrometastases.

A diagnostic challenge, in the clinical practice of the pathologist, is the identification of secondary gastric tumors. The heterogeneity of primary GC often prevents the identification of a metastatic gastric tumor. Therefore, we conducted a case study and a detailed literature review, in order to outline the histological characteristics and IHC profile of the primary tumor versus gastric metastasis. A particular aspect considered the possible involvement of EMT in the gastric metastasis process.

The original part of this work represents, from the CRC perspective, the use of specific IHC antibodies to identify an intermediate molecular subtype, called hybrid, in the light of the changes observed only in the tumor buds (loss of E-cadherin in tumor buds and/or translocation of membrane expression of β-catenin from the tumor center to nuclear expression in the buds), with an unchanged epithelial immunophenotype in the center of the tumor. The identification of this subtype, however, shows that it exhibits similar behavior to the epithelial subtype and the tumor aggressiveness is rather characteristic of the mesenchymal subtype.

Another original aspect of this paper is the method used for SLN mapping in GC cases, by completing the in vivo detection technique with ex vivo mapping, a method that led to the identification of SLN-only metastases in 26% of the examined cases. Although the stage of the tumor was completely changed, by identifying "aberrant" metastases (skip metastases) in only two cases, the identification led to adequate oncological therapy. The case study, although seemingly insignificant, triggers an alarm signal related to the pitfalls of histopathological diagnosis and forces a detailed histological examination, correlated with appropriate clinical and imaging examination.

From the clinical point of view, within the thesis, the protocol for quantifying the tumor buds with Maspin, already used in our laboratory in daily diagnosis, was developed.