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CRAIOVA
DOCTORAL SCHOOL**

DOCTORAL THESIS

***CONTRIBUTIONS TO COLON CANCER'S
IMAGISTIC AND MORPHOLOGICAL STUDY***

ABSTRACT

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KEY WORDS: colo-rectal cancer, carcinogenesis, endoscopy, surgical excision, morphopathology, statistical analysis, architectural patterns, correlations.

INTRODUCTION

Colo-rectal cancer is a priority issue in the digestive tract malignant pathology and is a real challenge in the development of diagnostic and therapeutic strategies.

In this study, we believe that improving morphopathological diagnosis by qualitative histological analysis using staining techniques and also objective analysis, quantitative at both optical and ultrastructural level using computer-assisted morphometry techniques, both pre- and postoperatively on exploration of endobioptic piece correlated with the analysis of the excision piece may lead to a better assessment of the evolutionary status of the tumor, improving the prognosis of these patients.

STATUS OF KNOWLEDGE

In the process of carcinogenesis there are several stages of development caused by genetic and epigenetic changes, as well as environmental factors intervention. Until not long ago it was considered that there are two types of CRC, totally different from each other: CRC hereditary or family, where germinal mutations transmitted autosomal hereditary occur and non-hereditary or sporadic CRC where sporadic type mutations occur, and the environmental factors contribute additional to phenotypic expression of malignancy.

Currently, it is argued that they arise from benign adenomatous precursors, being fed by mutations that increase the malignant behavior. Mutations that lead to the activation signal of "Wnt" path are basically those initiating event, then there are two other possible ways that contribute to the accumulation of additional mutations, the chromosomal instability path and the DNA mismatch repair (Mismatch repair).

Histopathology of the primary tumor has negative prognostic significance proven only for special types of adenocarcinomas: mucinous carcinoma, squamous cell "in signet ring", small cell carcinoma and squamous carcinoma.

For colon cancer classification multiple systems are used, the most satisfactory being considered classification / staging TNM (Tumour, Node, Metastases) - which is made at the proposal of UICC (Union Internationale Contre le Cancer) and AJCC (American Joint Commission of Cancer) and takes into account the three component elements.

The differentiation refers to the property that the cancer cells are more or less similar to the normal cells, both morphological and functional, the absence of

differentiation is called anaplasia. In general, the growth rate of the tumors is correlated with their differentiation level and, therefore, the majority of malignant tumors grow faster than the benign tumor. The notion of degree of differentiation, add the above mentioned one important prognostic factor.

Given these considerations and the fact that the certainty diagnosis in tumor pathology is based on histopathological examination of affected tissue, a classification on central morphological criteria remain the most satisfactory.

PERSONAL CONTRIBUTIONS

OBJECTIVES OF THE RESEARCH STUDY

The topic under discussion is of great interest and concern, both due to the need to identify both the algorithm of early diagnosis and prognostic factors necessary to specify the most effective therapeutic strategies.

The major objective - of the research project is to provide data for the assessment of pathological type and of stage (invasion) tumor according to the macroscopic appearance of the endoscopic lesion and also the need to support the initial morphopathological diagnosis after the analysis of the piece excision.

MATERIAL AND METHODS

The base for this study was composed of a group of 104 patients admitted to the Emergency County Hospital Craiova, in the Departments of Surgery I – II – III, during 2010 – 2013 – aiming to be a prospectively type of study.

The fragments of tumor tissue were subjected to conventional histology techniques for processing (fixation and paraffin including) after which serial sections were made for each block were stained with the dye conventional methods.

RESULTS

CLINICAL PROFILE

The analysis of clinical parameters evaluation results in the two groups of epithelial malignancies developed in the colon suggested the outline of different profiles in the two tumor types.

⇒ Tumors with a single morphological aspect

Malignant epithelial proliferation which had one architectural aspect within tumor were found predominantly in men with urban origin. Maximum incidence was present for men around an average age of 65, and was significantly lower compared to the age of the women who have developed such colo-rectal malignancy.

⇒ Tumors with two morphological aspects

On the other hand, the tumors with two dominant histological tumor mass, were found generally on older patients (average = 70 years), and often a woman with a balancing trend in the area of origin.

ENDOSCOPIC PROFILE

After analyzing all the parameters in the two groups endoscopy revealed that tumors with a single architectural histopathological appearance in the tumor mass were found mainly in the rectum, followed in descending order by the rectosigmoidian territory and the sigmoid. Usually have occupied the entire lumen of the colon without a very good completion reporting mezou belonging tumor. Generally experienced larger dimensions than the second group, with predominance ulcerated exofitic formations. Dominant histologic pattern was most common form of Well Differentiated adenocarcinoma pattern, and second place being awarded Grade 2 tubular differentiation.

Compared however, in the two morphological aspects group, the order is equivalent to the latter by increasing of cases of Moderately Differentiated forms which reach the same numerical value as Well Differentiated forms.

On the other hand, tumors of two histological architecture within the tumor mass, although still predominantly in the distal colon, have been found in increased numbers in its proximal region, most commonly in relation to the fixed edge (mezostenical), with smaller dimensions compared to group I, expressing particular protrusion into the lumen and with ulceration on tumor surface (UV form).

MORPHOLOGIC PROFILE

Overall, the biological behavior of tumors with a single morphological architecture was a somewhat less aggressive, with invasion of the entire wall, but without exceeding serosa in most cases, less frequent invasion of private parietal structures and lymph nodes regional and lower metastases.

The analysis of two morphological aspects tumors revealed a more aggressive biological behavior with fully invasion of the wall and overcome it completely, affecting intraparietal blood vascular structures in the presence of tumor embolism, especially with regional lymph invasion which was almost a rule.

Regarding the Degree of Differentiation of tumor proliferation, whether it was tumor that was about one architectural pattern or tumor with two architectural patterns, it did not correlate with any of the major morphological indicators of tumor

aggressiveness investigated namely colic wall invasion depth (pT) or invasion of regional lymph nodes (pN). In other words, the degree of differentiation of the malignant cell population does not affect its degree of aggressiveness.

It should be mentioned that, due to the absence from the sheets of the evaluation of the level of metastasis observed in more than 80% of the cases, the correlation with that aggression indicator has not been possible and, accordingly, nor the correlation with TNM overall score.

Overall, the two individualised types of tumors in the study group showed enough features that distinguish them primarily in terms of biological behavior, so that allow us to define them as two separate entities.

CORRELATION PROFILE BETWEEN TYPES OF MORPHOLOGICAL STUDY

The comparative analysis of morphopathological diagnoses endoscopically established (the fragment of biopsy) and of the operated piece revealed several aspects to be taken into account in the final evaluation of a patient with malignant proliferation of epithelial colo-rectal.

Overall, we can say that the two morphological assessment methods of colo-rectal tumors were correlated with each other, compliance being beyond, for most evaluation parameters 70 percentage.

Finally, the biopsy histopathological diagnosis of the biopsy piece is still for guidance, the final morphological evaluation is reepresented by th histopathology examination of surgical excision piece.

CONCLUSIONS

Our study including both individual and comparative analysis of a significant set of clinical and morphological parameters has led to several conclusions that may be of importance and applicability in future handling of colo-rectal carcinoma in medical practice:

1. A first fact to be highlighted is the particularity of general group of patients included in the study was the prevalence of cases with tumors at an advanced progressive stage, particularity attested by the local and regional level extension of neoplastic proliferation.
2. The first findings of microscopic morphological evaluation of malignant epithelial proliferations lot located in the different segments of large intestine was that of individualization of two distinct groups by way of provision of neoplastic cells throughout the tumor mass namely a much larger group where the proliferation of neoplastic cell had a uniform architecture and a

less numerous group where the arrangement of malignant cells was a heterogeneous, with at least two patterns of arrangement.

3. Comparative analysis of a set of descriptive clinical and morphological parameters led to a second finding, namely that the complexity degree of tumor architecture has helped shape two distinct profiles for the two types of colorectal carcinomas:
 - A clinico-morphological profile of tumors with a single architectural pattern was that of a man aged about 65 years, resident in urban areas who presented mostly in the terminal segments of the colon a tumor formation with ulcero-vegetant type, generally large sized and with circumferential invasion of colic wall or located in the free zone, which on histopathological examination proved to be usually a common form of adenocarcinoma moderately differentiated, rarely with inflammatory reaction peri and intratumoral and outbreak of intratumoral necrosis, tumor that invaded the colic wall entirely without significantly expand into loco-regional lymph nodes.
 - Another clinical and morphological profile of tumors with two architectural patterns was that of an elderly man, about 70 years, who presented a smaller tumor with ulcero-vegetant look, localized in a significant number cases also on the proximal segments of the colon, usually circumferential extension or fixed location in the area this time where the histopathological examination revealed a common form of adenocarcinoma, usually well-differentiated in tumor areas from colic lumen and a pattern architectural poorly differentiated or mucinous to the outer layers of the wall more frequently accompanied by inflammatory phenomena and areas of intratumoral necrosis and obviously more aggressive behavior, as evidenced by the identification of regional lymph node invasion.
4. Another finding worthy of being chosen was that in any of the two groups of tumors analyzed, both at the architectural pattern monomorphic and the more complex architecture tumor, the statistical correlation assessment showed that the degree of differentiation of proliferation tumor does not appear to directly and significantly influence its aggressive nature expressed through the colic wall invasion and extension to the regional lymph nodes.
5. The results of comparative analysis of preoperative pathological evaluation using endoscopic investigation accompanied by microscopic examination of the targeted biopsy piece and macro and microscopic assessment of the

operated piece highlighted the important role of endoscopy in the management of patients with colo-rectal malignant proliferation.

6. The lower concordance degree regarding the evaluation of macroscopic appearance, especially in terms of assessing the degree of tumor differentiation are not able to diminish the role and value of preoperative endoscopic investigation as long as, especially in the latter case, even the present study of to the degree of differentiation revealed that it has no effect on the biological behavior of the tumor which means that in case of multiple tumors architectural patterns, for example, which has been found to be more aggressive not to be so important that the bioptic examination does not provide an adequate assessment of the degree of differentiation.
7. Improved imaging techniques, in particular increasing the ability to obtain a fragment as consistent as possible both from mucosal and from the colon wall by endoscopic biopsy, will allow a better preliminary assessment of colo-rectal cancer.
8. Difficulties in assessing patients with colorectal cancer can be reduced in the context of effective collaboration within a multidisciplinary team consisting of an internist / gastroenterologist, radiologist, surgeon and pathologist by applying an investigation algorithm correctly structured.

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