PhD Thesis

CLINCO-PATHOLOGICAL FACTORS WITH PROGNOSTIC AND PREDICTIVE IMPACT IN COLORECTAL NEOPLASMS

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SUMMARY

Colorectal cancer (CRC) represents a significant fraction of all cancer deaths, with 1 in 10 deaths in 2018 being caused by CRC. The highest incidence of colon cancer is found in Hungary and Slovenia, followed by Australia, New Zealand and North America. In Romania, CRC is the 4th leading cause of death from cancer, after breast, prostate and lung cancer. Given the multidisciplinary nature of colorectal cancer treatment and considering that neoplastic disease is a biological problem and not a statistical one, we turned our attention to the study of those parameters that could have a prognostic role for patients. The final goal is, of course, an individualized treatment, with a higher chance of success, depending on the particularities of these prognostic and predictive factors. In this paper we proposed the interdisciplinary approach of the prognostic features of CRC in two distinct chapters.

In the first main chapter of we approached CCR from a surgical point of view. We focused on a surgical option with a low degree of penetration in Romania, namely intersfincteric resection (SRI) - a technical option adapted for patients with rectal cancer who refused a surgery that ends with a colostomy bag. The main benefit is the lack of colostomy or ileostomy, even temporary, which translates into increased quality of life of the patient (QoL). We started from the premise that this type of surgery can provide oncological results superimposable with those of classical interventions and satisfactory functional results, both in the short and long term. We present the prospective aspects of 60 consecutive patients that underwent this modified version of ISR.

In the second main chapter we added data related to the histopathological aspects of RCC. Because clinical casuistry has led to the identification of histological subtypes of gastrointestinal carcinomas, for which therapeutic protocols are not yet elucidated and histopathological diagnosis is difficult to establish, we proposed the immunohistochemical examination (IHC) of a carcinoma with a particular phenotype, seldom found in clinical practice. We thus considered a carcinoma composed of adenocarcinoma and neuroendocrine carcinoma, each representing over 30% of the tumor and called mixed carcinoma, adenoneuroendocrine (MANEC). We hypothesized that these carcinomas, located in the gastrointestinal tract, have a somewhat different histogenesis and behavior from classical adenocarcinoma and we tried to prove this hypothesis by the immunoprofile tumor cells of the two components. Considering the mentioned premises, the main objective of the thesis was to demonstrate the oncological and functional feasibility of “SRI - modified technique” and to examine the histogenetic and evolutionary peculiarities of gastrointestinal MANECs.

Results Chapter I: the median age was 66.50 ± 10.72 years, with values between 42-81 years. Thus, 56 patients (93.33%) were over 50 years old. In terms of patient gender, 31.67% (n = 19) were female while 68.33% (n = 41) were male, with an M: F ratio of 2: 1. As a tumor location, 38 (63.33%) patients had carcinomas located in the lower rectum, 20 (33.33%) were diagnosed in the middle rectum and two cases (3.33%) anal canal. The location of the tumor taken into account for statistical processing

was the one corresponding to the final anatomopathological examination (macroscopic orientation) and not the intraoperative one. The median value of tumor diameter was 30 ± 14.01 mm, with a minimum of 4 mm and a maximum of 70 mm. In 47 patients (78.33%) we performed partial SRI and total SRI was performed in 13 patients (21.66%). Mesorectal excision was complete or satisfactory in 54 cases (90%), with negative CRM in 95% of cases (n = 57). The mean duration of surgery was 160 ± 18 minutes, with an intraoperative blood loss of 140 ± 55 ml.

Postoperative complications

We identified postoperative complications in 10 (16.67%) patients. The most common complication was muco-submucosal necrosis of the telescopic colonic segment, Clavien-Dino type I complication, found in five cases. This complication occurred on average at 11 days following surgery.

Survival rate

The survival rate was 86.7% (8 deaths at 12 months), 80% (12 deaths at 24 months), 76% (14 deaths at 36 months, and 67.5% (18 deaths) at 60 months following surgery. The mean survival was 70.97 (± 5.17) with a 95% confidence interval, and after statistical processing, based on batch size, we obtained an estimated survival of 21% (± 0.16) at 8 years postoperatively.

Results chapter II: a retrospective analysis of Târgu-Mureș County Emergency Clinical Hospital records found that MANEC tumors represent 2.5% of the total gastric carcinomas and 1.16% of the total CRC. We found a total of 13 cases. MANECs were diagnosed in both men and women, with a mean age of 63.55 ± 12.13 years (minimum 46 and maximum 78 years). Of the 13 patients, only four had a survival of at least 20 months postoperatively, which did not necessarily depend on the depth of the tumor invasion: a localized cecal case – pT4N0 stage, a rectal one – stage pT1aN1 and two cases of gastric MANEC diagnosed in stages pT2N0 respectively pT3N0. In the primary tumor, each component accounted for over 30% of the tumor and the adenocarcinoma component had, in some cases, a mucinous component. In lymphatic metastases, we identified both purely neuroendocrine and mixed architecture (adenocarcinoma and neuroendocrine), regardless of tumor location. We have not identified cases in which lymph node metastases are represented by pure adenocarcinoma.

Conclusions:

• From an oncological point of view, for lowe rectal cancer, ISR presents good results, superimposable with those from other “non-sphincter saving” interventions.

• following ISR survival is lower in patients over 50 years of age, diagnosed in locally advanced stages, even when performing proper total excision of the mesorectum.

• Direct coloanal anastomosis after partial or total ISR can be used with the abandonment of temporary ileostomy / colostomy without exposing the patient to major complications.

• Mucos-submucosal necrosis is one of the possible complications that can be treated on an outpatient basis, without the need for a second surgery.

• functional results following ISR are good, with a satisfactory long-term continence

• The Wexner score is a good tool for both the patient and the surgeon to assess pre- and postoperative fecal continence. This score can guide the choice of surgical technique.

• Epithelial-mesenchymal transition is not a phenomenon involved in the genesis and aggressiveness of mixed adenoneuroendocrine carcinoma (MANEC), diagnosed in the gastrointestinal tract

• Maspin is not a marker with potential diagnosis, prognosis or predictive, in colorectal MANEC

• CD44 may influence the biological behavior of gastrointestinal MANEC

• Therapeutic management of patients with MANEC is necessary to take into account its histological features, both in the primary tumor and in lymph node metastases