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ORIGINAL ARTICLE

Evaluation of clinical, morphopathological and therapeutic prognostic factors in rectal cancer. Experience of a tertiary oncology center

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Summary

Purpose: *Morphopathological factors continue to be the most important prognostic factors in colorectal cancer, but there is evidence regarding the prognostic value of some factors that are not yet used in current clinical practice. The purpose of the present study was to evaluate the most important clinical, morphopathological and therapeutic prognostic factors in rectal cancer.*

Methods: *This study retrospectively analyzed 317 patients diagnosed and treated at the Ion Chiricuta Institute of Oncology between 2000-2008. The prognostic value of 13 variables was analyzed and correlations between them were established. Nine variables were included in a multivariate analysis model.*

Results: *The 5-year overall survival (OS) was 55.6%, significantly higher for patients with TNM stage I disease (71.7%), compared to stage II (71.4%), stage III (45.4%) and stage IV (12.5%; p<0.001). In multivariate analysis, the independent prognostic factors were tumor stage, age, lymph node invasion, venous, lymphatic and perineural invasion.*

Conclusions: *In addition to the TNM stage and lymph node invasion, age, venous, lymphatic and perineural invasion were also proved to have prognostic significance in rectal cancer. Further studies are required for the validation of prognostic assessment models in patients diagnosed with rectal cancer.*

Key words*: lymphatic invasion, perineural invasion, prognosis, rectal cancer, TNM stage, venous invasion*

Introduction

Colorectal cancer (CRC), the most common malignancy of the gastrointestinal tract, is the third most frequent cancer in men and the second in women. In Romania, the incidence of CRC is continuously increasing and in terms of mortality, this disorder has become the second leading cause of death from cancer, after lung cancer [1]. Despite many efforts made to detect the disease at an early stage, the long-term prognosis of CRC has not significantly changed over the last decade, with a 5-year OS of 60% [2].

Personalized treatment for colorectal cancer is a necessity. In this sense, predicting its prognosis is vital for choosing appropriate therapeutic interventions. Histopathological factors continue to be the most important prognostic factors in CRC according to the staging proposed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) [3].

Published studies demonstrate the prognostic value of some factors that are not yet applied in current clinical practice [4].

The purpose of this study was the evaluation of the most important clinical, morphopathological and therapeutic prognostic factors in rectal cancer.

Methods

Of the 563 rectal cancer patients hospitalized at the Ion Chiricuta Institute of Oncology between 2000-

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2008, after applying the exclusion criteria (lost to follow-up at the first admission, double location, initial treatment in another service, incomplete information, histological type other than adenocarcinoma, rectal metastases), only 317 cases were loft for study. Patient data were obtained from clinical observation records and registry of Ion Chiricuta Institute of Oncology, Cluj-Napoca, with the approval of the Hospital Ethics Committee. Data on mortality were obtained from the Cluj-Napoca Civil Registry.

The prognostic factors analyzed were clinical (age, sex, bowel obstruction at presentation), morphopathological (radial resection margin, TNM stage, lymph node invasion, number of resected lymph nodes, venous invasion, lymphatic invasion, perineural invasion, histologic tumor grade), and therapeutic (response to neoadjuvant radiotherapy or radiochemotherapy, type of surgery).

TNM staging of patients was reviewed according to the 7th edition of the UICC/AJCC Cancer Staging Manual. Using histologic tumor grading, the cases were divided into two groups, low tumor grade (well and moderately well differentiated tumors), and high tumor grade (poorly differentiated and undifferentiated tumors).

Response to neoadjuvant radiotherapy or radiochemotherapy was quantified as follows: complete or almost complete response (when postoperative T stage was 0 or 1, or N stage was 0), incomplete response (when postoperative T stage was higher than 1 but lower than the initial T stage), and no response (when postoperative T stage was the same as the initial T stage).

The patients were followed up from the date of treatment initiation (surgery or neoadjuvant therapy) to the date of the last information. The study was completed in August 2011.

Statistics

For statistical analysis, the R environment for statistical computing and graphics, version 1.15.1, was used. Data analysis was descriptive and inferential for each data set, according to its characteristics. Thus, the Student's t-test, Mann Whitney U test, Kruskal-Wallis test and Spearman's correlation coefficient were used. Survival data was compared using the Kaplan-Meier survival curves, the log-rank test, and Cox regression analysis. For all tests, the bilateral statistical significance threshold was $p < 0.05$.

Results

All 317 patients included in the study had rectal adenocarcinoma. Of these, 201 (63.4%) were male. Most of the patients (63.4%) were aged between 50 and 70 years, with a mean age of 54 years.

More than half of the patients (58.8%) had advanced-stage disease (stages III and IV). All patients underwent surgery and in 74.4% of the cases, surgery was performed as a first-line treatment. Eighty one patients (25.5%) received neoadjuvant radiotherapy or radiochemotherapy, and 236 patients (74.4%) adjuvant radiotherapy, chemotherapy or both. Descriptive statistics of the characteristics of the patients is shown in Table 1.

The 5-year OS and the progression-free survival (PFS) were 55.6% (95% CI, 0.50-0.61) and 53.4% (95% CI, 0.479-0.595), respectively. The 5-year OS was statistically significantly higher in patients with stage I disease (71.7%), compared to stage II (71.4%), stage III (45.4%) and stage IV (12.5%; $p<0.001$).

Regarding the number of resected lymph nodes, two linear regressions between the location from the anus/the number of resected lymph nodes and age/the number of resected lymph nodes were determined, without finding a correlation between these ($r=0.16$, $p=0.058$; $r=0.06$, $p=0.297$, respectively).

The association between venous, lymphatic and perineural invasion and other morphopathological factors known to have a negative impact on the prognosis of rectal cancer such as tumor recurrence, histologic tumor grade, TNM stage, number of positive lymph nodes and distant metastases, presented in Table 2, was studied.

Cox multivariate analysis depending on age, TNM stage, histologic tumor grade, lymph node invasion (pN stage), venous, lymphatic and perineural invasion, the type of surgery and neoadjuvant treatment response was performed and the data are shown in Table 3.

Discussion

The incidence of CRC is continuously increasing [5] and although improvement in prognosis has lately been observed [6], only 50-60% of patients survive at 5 years [2,7,8]. Thus, formulating an accurate prognosis in CRC is essential to the choice of individualized treatment options. Although many studies have been published in this regard, the treatment of CRC has not undergone significant changes.

Despite the fact that there are differences in the etiology and epidemiology of colon cancer and rectal cancer, most of the published studies choose to investigate cases of combined colon and rectal cancer.

However, a better understanding of these diseases shows that the differences between them

Table 1. Descriptive statistics of the clinical, morphopathological and therapeutic prognostic factors

Clinical prognostic factors	*Patients, N*	*%*	*5-year OS (%)*	*p value*
Sex				
Male	201	63.4	57.80	0.381
Female	116	36.6	51.30	
Age (years)				
< 50	48	15.1	63.90	0.032
50-70	201	63.4	57.30	
>70	68	21.5	43.70	
Bowel obstruction at presentation				
Yes	26	8.2	52.80	0.254
No	291	91.8	55.80	
Morphopathological prognostic factors				
Radial resection margin (cm)				
> 2	56	17.7	66.40	0.038
≤ 2	261	82.3	52.80	
TNM stage				
I	56	17.6	71.70	<0.001
II	75	23.6	71.40	
III	178	56.3	45.40	
IV	8	2.5	12.50	
Lymph node invasion (pN)				
pN0	165	52	70	<0.001
pN1a	34	10.7	48	
pN1b	48	15.1	36.80	
pN2a	39	12.3	34.10	
pN2b	31	9.9	20.50	
No. of examined lymph nodes				
<12	212	67	54.30	0.955
≥12	105	33	56.40	
Venous invasion				
No	251	79.2	60.40	0.01
Yes	66	20.8	37.40	
Lymphatic invasion				
No	174	55.9	64.60	<0.001
Yes	143	45.1	45	
Perineural invasion				
No	257	81	59.15	0.014
Yes	60	19	39.19	
Histologic tumor grade				
Low	286	90,2	56.90	0.019
High	31	9.8	41.10	
Therapeutic prognostic factors				
Neoadjuvant treatment response				
Complete/almost complete	48	59.2	68.70	0.041
Incomplete	14	17.3	39.10	
No response	19	23.5	47.60	
Type of surgery				
Dixon anterior resection	161	50.7	57.20	0.018
Miles resection	142	44.8	56.10	
Hartmann resection	144	4.5	28.50	

have an important influence on the approach of the two neoplastic processes.

All patients underwent surgery. Curative resection (R0) was performed in 250 patients (78.8%), 39 patients (12.3%) had microscopic residual tumor (R1), and 28 patients (8.9%) had macroscopic residual tumor tissue (R2).

Data published in the literature show a 5-year OS rate of 66% in patients with rectal cancer [9]. In our study, the 5-year OS was 55.6%.

Although CRC is generally not considered a hormone-dependent malignancy, epidemiological studies in women have shown that the increase of female hormones due to pregnancy or use of exogenous steroid hormones is associated with a lower risk of developing CRC [10,11], while some studies have shown an improved survival rate in women who develop the disease [12,13]. The present study demonstrated an almost double incidence of rectal cancer in men compared to women (201 vs 116), which is consistent with the literature data. Regarding the prognosis of patients after therapy, we did not find a significant difference in OS between the two sexes. This can be explained by the fact that in this study, 84% of women were aged over 50 years, with an increased chance of being postmenopausal, consequently lacking the supposed protective role of female steroid hormones. Similar results have recently been reported, which describe similar gender-related differences for all stages of CRC, with a better survival rate in young female patients compared to male patients, differences that are reversed in postmenopausal female patients compared to male patients of the same age [14,15].

Rectal cancer is a disease of middle-aged and elderly people, the risk increasing with age. Although the overall incidence of this type of cancer is low in people under 40 years old (3-10%),

Table 2. Association between venous invasion, lymphatic invasion, perineural invasion and other morphopathological factors

	Venous invasion			*Lymphatic invasion*			*Perineural invasion*		
Factors	*Yes (%)*	*No (%)*	*p value*	*Yes (%)*	*No (%)*	*p value*	*Yes (%)*	*No (%)*	*p value*
Tumor recurrence									
Local/distant	18 (29.5)	43 (70.5)	0.057	45 (73.7)	16 (26.3)	<0.001	25 (27.8)	65 (72.2)	0.03
Tumor grade									
Undifferentiated	0 (0)	1 (100)	0.011	0 (0)	1 (100)	<0.001	0 (0)	1 (100)	<0.001
Poorly diff.	15 (50)	15 (50)		25 (83.3)	5 (16.7)		12 (40)	18 (60)	
Moderately diff.	44 (20.3)	173 (79.7)		106 (48.8)	111 (51.2)		44 (20)	173 (80)	
Well diff.	7 (10.1)	62 (89.9)		12 (17.4)	57 (82.6)		4 (5.8)	65 (94.2)	
TNM stage									
I	5 (8.9)	51 (91.1)	<0.001	7 (12.5)	49 (87.5)	<0.001	6 (10.7)	50 (89.3)	<0.001
II	6 (8)	69 (92)		11 (14.6)	64 (85.4)		9 (12)	66 (88)	
III	53 (29.7)	125 (70.3)		118 (66.3)	60 (33.7)		41 (18.7)	137 (81.3)	
IV	2 (25)	6 (75)		7 (87.5)	1 (12.5)		4 (50)	4 (50)	
Number of positive lymph nodes	-	-		3 (1-5)*	0	<0.001	2.5 (0-5)*	0 (0-2.5)*	<0.001
Distant metastases									
M0	64 (20.7)	245 (79.3)	<0.001	136 (44)	173 (56)	<0.001	56 (18.1)	253 (81.9)	0.003
M1	2 (25)	6 (75)		7 (87.5)	1 (12.5)		4 (50)	4 (50)	

*range

Table 3. Cox multivariate analysis

	Hazard ratio	*p value*	*95% confidence interval*
Age	1.03	0.0007	1.01 - 1.04
TNM stage	0.44	0.0142	0.22 - 0.84
Histologic tumor grade	1.32	0.1159	0.93 - 1.86
Lymph node invasion (pN stage)	1.67	0.0135	1.11 - 2.50
Venous invasion	0.56	0.0174	0.34 - 0.90
Lymphatic invasion	1.2	0.0001	1.09 - 1.31
Perineural invasion	0.6	0.0082	0.41 - 0.87
Type of surgery	2.009	0.065	0.95 - 4.21
Neoadjuvant treatment response	1.285	0.490	0.64 - 2.57

recent data suggest an increase in incidence by up to 75% [16]. We found a 3% incidence of rectal cancer in young patients (under 40 years of age), at the lower limit of the reported data. By dividing the patients by age groups (under 50 years, between 50 and 70 years, and over 70 years), we obtained a significantly better OS in younger patients, which decreased with age.

A possible complication of rectal cancer is bowel obstruction, which in some studies is considered an independent negative clinical prognostic factor [17,18]. Of the 317 patients included in our study, only 26 (8.2%) had bowel obstruction at presentation, of which 10 received neoadjuvant treatment and 16 underwent primary surgical resection. Although the 5-year OS was slightly higher in patients without bowel obstruction (55.8% vs 52.8%), our results were not statistically significant (p=0.254).

Radial resection margin has a significant impact on the prognosis of local recurrence rates, distant metastases and survival in CRC, and is also important in the selection of patients for adjuvant therapy. We identified 67 patients (21.13%) with positive resection margins who received postoperative adjuvant therapy.

The most important prognostic indicators are expressed by the TNM stage. The majority of the patients in this study were diagnosed with stages III and IV disease (58.8%), which emphasizes

the need to implement a more efficient screening program. Similar 5-year overall survival rates for stages I and II disease might be due to the existence of a subgroup of stage I patients with a poorer prognosis (because of tumor histopathological and molecular characteristics associated with a more aggressive phenotype) or to a better prognosis of stage II patients as a result of adjuvant treatment.

Lymph node invasion as well as the number of positive lymph nodes are predominant predictive indicators in CRC and the leading indication for adjuvant therapy. The number of surgically resected and histopathologically evaluated lymph nodes influences the accuracy of staging and oncologic outcomes, both in patients with positive and negative lymph nodes. Although the recommendation of the 7th edition of the AJCC Cancer Staging Manual is to resect a minimum of 10 to 14 lymph nodes (with an average of 12 lymph nodes), this aspect is still controversial [19]. Those who are against the establishment of a lymph node resection limit argue that the number of lymph nodes that can be resected is strongly influenced by other factors (particularly patient age, race/ethnicity, tumor location and its biological characteristics like TNM stage, presence of microsatellite instability, TGFb and interleukin-10). Some published studies show a decrease in the number of the resected lymph nodes with age [20,21] or with the progression of tumor location from the right colon to the left colon and rectum [22,23]. The present study did not find an association between the number of resected lymph nodes and the distance of the tumor from the anus or patient age. We believe that the aim should be to resect as many lymph nodes as possible, although the excision of a very large number of lymph nodes can sometimes be unjustified. The average number of lymph nodes resected in our study was 27 (range 1 to 53); in 67% of the cases, at least 12 lymph nodes were resected. Published evidence suggests that the number of resected lymph nodes is a prognostic factor in CRC [24]. We investigated the prognostic value of a minimum of 12 resected lymph nodes in terms of survival, without finding a statistically significant difference.

Lymph node invasion was an independent negative prognostic factor in rectal cancer in the present study. The results of this study, in accordance with known evidence in the latest edition of the AJCC Cancer Staging Manual, divided the N classification into several subgroups depending on the number of positive lymph nodes, in order to meet the current need to define subgroups of patients with different prognoses, for an individualized management of patients with CRC.

Venous invasion in our study was seen in 66 patients (20.8%) and was demonstrated to be, in accordance with current data, a negative prognostic factor [25]. However, the presence of venous invasion might be underdiagnosed here, because no specific staining for elastin was used to facilitate its identification. In the absence of distant metastases, the presence of venous invasion can be a useful means of selecting patients who might benefit from adjuvant chemotherapy.

Lymphatic invasion is another recognized negative prognostic factor in CRC [26]. We identified 143 patients (45.1%) with rectal cancer who presented with this histopathological characteristic. The presence of lymphatic invasion could be taken into account for the selection of patients at high risk who might benefit from a more aggressive therapy. However, recent studies suggest that in patients with rectal cancer and positive lymph nodes, lymphatic invasion does not affect prognosis [27].

Perineural invasion is a distinct neoplastic process, which can be seen in the absence of vascular or lymphatic invasion. Its role as a prognostic factor in rectal cancer is still controversial in the literature, although there is evidence that it influences both OS and PFS [28]. Perineural invasion has a variable incidence in CRC, different studies reporting values between 10-33%. We found an incidence of 19% (60 patients), which is consistent with these values. Our results could be slightly underreported due to technical difficulties encountered by the pathologist in the identification of perineural invasion, such as the presence of inflammatory cells or large mucinous areas that hide the presence of tumor cells around the nerves [29]. In our study, rectal cancer patients with perineural invasion had advanced disease stages (III, IV) ($p<0.001$), high-grade tumor differentiation ($p<0.001$), distant metastases ($p=0.003$), positive lymph nodes ($p<0.001$), local recurrences ($p<0.01$), and distant recurrences ($p<0.03$) more frequently. Although the risk of distant metastasis is higher in patients with perineural invasion, in accordance with other studies, our study included only 8 patients with distant metastases at the time of diagnosis. The impact of perineural invasion on OS is also significant, with an average of 42 months vs 93 months in patients without perineural invasion ($p=0.014$). In multivariate analysis, the presence of perineural invasion proved to be an independent prognostic factor for OS. Pa-

tients with perineural invasion could be a distinct subgroup that might benefit from a more aggressive therapeutic approach.

A particular situation is that of patients with negative lymph nodes but with perineural invasion. Lymph node invasion is an established indication for adjuvant treatment in CRC, while patients without positive lymph nodes do not currently benefit from such treatment. However, there is a subset of patients without lymph node metastases who have poorer results, with early locoregional recurrence and a lower OS. Liebig et al. [30] suggested that the poorer prognosis of this subgroup of patients could be explained by the presence of perineural invasion. In our study, we did not find a significant difference in this regard (the 5-year OS for patients with negative lymph nodes and positive or negative perineural invasion was 68.42% and 69.92%, respectively, p=0.82).

High histologic tumor grade proved to be a negative prognostic factor for rectal cancer, as shown also by other authors [26], associated with reduced OS (p=0.019), but not an independent factor in Cox multivariate analysis (p=0.1159), being limited in our study by the relatively small number of patients with high tumor grade.

Treatment of rectal cancer is - in the first place - surgical, with curative potential. The chosen type of surgical intervention depends on the stage and location of the tumor. All patients included in our study were operated (81 cases after neoadjuvant therapy). In 50.7% of the cases, Dixon anterior resection was performed, 44.8% of the cases underwent Miles abdominoperineal resection, and in 4.5% of the cases Hartmann resection was carried out. The 5-year OS was similar for Dixon and Miles resection (57.2% vs 56.1%), while, as expected, in patients with Hartmann resection, the OS was lower (28.5%, p=0.018). The type of surgical intervention was not independent factor in multivariate analysis.

Neoadjuvant chemoradiotherapy in rectal cancer is associated with improved local control and can lead to complete tumor regression. A recent study showed that neoadjuvant chemoradiotherapy improves local PFS in locally advanced rectal cancer [31]. Another study suggests that response to neoadjuvant chemoradiotherapy has a predictive value in CRC [32]. Modern neoadjuvant chemoradiotherapy schemes were associated with a complete response rate of 20% [33,34]. Concerning the neoadjuvant treatment, 26 patients (8.2%) underwent radiotherapy, 2 patients (0.6%) received chemotherapy, and 53 patients (16.7%) received chemoradiotherapy. Complete response was achieved in 2 cases (0.6%) of the 81 patients who underwent neoadjuvant chemoradiotherapy. Thus, in order to study the impact of neoadjuvant chemoradiotherapy on the prognosis of rectal cancer, we defined three groups: group 1 - with complete or almost complete response (59.2%), group 2 - with incomplete response (17.3%), and group 3 - with no response (23.5%). In groups 1, 2 and 3 5-year OS after surgery was 68.7%, 39.1% and 47.62%, respectively, which is lower compared to relevant OS reported in the literature [35]. Response to neoadjuvant therapy was demonstrated to be a prognostic factor in rectal cancer in univariate analysis, but was not found to be independent predictor in multivariate analysis (p=0.490). However, there is a limitation of the present study with regard to neoadjuvant treatment. Although 186 (58.8%) of the patients in the study had advanced disease stages (stages III and IV), only 81 (25.5%) of them received neoadjuvant treatment. This can be explained by a possible underestimation of the T stage by the diagnostic imaging methods used.

Following univariate analysis, age, tumor stage, histologic tumor grade, lymph node invasion, the number of positive nodes, venous invasion, lymphatic and perineural invasion, the type of surgery and the response to neoadjuvant treatment significantly influenced the prognosis of rectal cancer. After including the variables in the multivariate analysis model, we found that only tumor stage, age, lymph node invasion, venous, lymphatic and perineural invasion significantly and independently influenced the long-term prognosis of patients with rectal cancer.

In addition to the TNM stage and lymph node invasion (already known in the literature as prognostic factors for rectal cancer), age, venous invasion, lymphatic invasion and perineural invasion were also demonstrated to have a prognostic value in rectal cancer. Being associated with a poorer prognosis, these factors should be taken into account to identify subgroups of patients who might benefit from more aggressive treatment. Further studies on the prognostic factors identified in this study are required for the creation and validation of prognostic assessment models in patients with rectal cancer.

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