Evaluation of prognostic factors for 5 year-survival after surgery for colorectal cancer

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AIM: *The aim of this study was to assess and analyze the prognostic factors for survival in patients undergoing curative surgery for colorectal cancer and to identify new prognostic factors.*
METHODS: *The prospective study included 301 patients diagnosed with colorectal cancer, stages I-III, undergoing curative surgery. Demographic data, clinical and anamnestic data, laboratory exams, paraclinical examinations, morphological and pathological examination were recorded. The Petersen index was calculated. Tumor necrosis, desmoplasia and mucinous component were assessed. Local inflammatory response was calculated using Klintrup criteria. Patients were followed for five years after surgery.*
RESULTS: *There were 197 patients (66.4%) who survived and 104 patients (34.6%) who died during the 5-year follow-up period. Multivariate analysis showed that death was mostly associated with patients over 60 years of age (p=0.05). Tumor location within the colon was associated with a better survival than tumor location within the rectum (HR - 0.57; p=0.02). Patients with T>2 had a poor prognosis compared to those with T=<2 (HR - 2.23; p=0.02). Patients with Klintrup score >1 had a better prognosis (HR - 0.20; p <0.001). Patients with venous invasion showed significantly worse prognosis (HR - 2.26; p=0.003). Patients with desmoplasia score 3 had lower death rates than those with score 1 (HR - 0.42; p=0.01).*
CONCLUSION: *Survival was superior in patients with cancer of the colon. The following parameters had a strong independent prognostic factor for survival: age, stage T>2, venous invasion, mucinous component and desmoplasia.*

KEY WORDS: Colorectal cancer, Prognostic factors, Survival

Introduction

Colorectal cancer is still a leading cause of death in developed countries without any significant improvement in survival rates in recent years. The incidence of colorectal cancer in Romania ranks third after breast and lung cancer. Colorectal cancer mortality in Romania ranks third after lung and breast cancer, data similar to those seen at European level [1,2].

Despite radical treatment, there are patients with high death rates five years after surgery. The incidence of colorectal cancer is increasing in Europe, with a figure of 499.7 (per 100,000) new cases for the end of 2018, with a mortality of 242.5. At European Union level, the incidence of colorectal cancer, for 2018, is 378.4 (per 100,000) with a mortality of 173.2 [1].

The patients that are at high risk can be identified by using the AJCC and UICC TNM staging systems, which are considered the most powerful prognostic parameters currently. Despite treatment, results in terms of survival

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differ, most likely due to the impact of certain prognostic factors that depend both on the patient and on tumor characteristics. Using new clinical and histopathological prognostic factors, we could identify candidates for a more aggressive treatment, followed-up closely to improve prognosis.

The prognostic factors that depend on the patient are represented by the host's overall inflammatory response to tumor aggression. These parameters can be identified by counting the number of leukocytes, the ratio of neutrophils to lymphocytes. There are also a number of tumor-related morphopathological factors that may have a prognostic role: venous invasion, peritoneal damage, tumor necrosis, and desmoplasia (fibrous tissue formation). An important prognostic role is played by mutations in suppressor genes (microsatellite instability) and oncogenes [3]. The local inflammatory response was identified by the presence of inflammatory infiltration at the level of the tumor invasion. For some of these parameters were calculated different prognostic scores.

The total number of invaded lymph nodes does not allow for precise staging of colorectal cancer and is required identifying other pathological markers that would allow for the exact staging to initiate and continue treatment [4]. The Limph node ratio (LNR) is defined as the ratio between the number of positive lymph nodes and the total number of lymph nodes resected. LNR was identified as an independent prognostic factor in stage III colorectal cancer [5]. The use of LNR along with the current TNM staging could predict better prognosis in patients with colorectal cancer.

The aim of the study was to evaluate the possible role of several variables (general inflammatory response, neutrophils to lymphocytes ratio, local inflammatory infiltrate, desmoplasia, mucinous component, LNR) as prognostic factors for 5 year-survival in patients undergoing curative surgery for colorectal cancer.

Materials and Methods

In order to achieve the objectives of the study, 301 patients admitted and undergoing curative surgery for colorectal cancer within the Surgical Clinic of the Municipal Hospital in Cluj-Napoca, the 5th Department of Surgery of "Iuliu Hatieganu" University of Medicine and Pharmacy between January 2002 and December 2011 were included in the study. All patients included in the study signed the informed consent form and the study was approved by the Ethics Committee of the Municipal Clinical Hospital, Cluj-Napoca.

The diagnosis of colorectal cancer was established preoperatively by clinical, laboratory and paraclinical examinations (chest X-ray, abdominal ultrasound, lower gastrointestinal endoscopy with biopsy). Patients who experienced the following conditions were excluded from the study: pre- or intraoperatively detected distant metastases, synchronous primary tumours, inflammatory bowel disease, patients with other histological types of cancer beside adenocarcinoma, patients who had been subjected to emergency surgery, who received preoperative radiotherapy, patients who died less than 30 days after surgery, patients with incomplete data and those who did not sign the informed consent form.

Data were recorded from observation charts, surgery protocols and pathology reports. A database was created, including demographic data (age, gender, origin), clinical and anamnestic data (symptoms, duration of symptoms, major comorbidities), laboratory exams (white blood cell count, lymphocyte count, neutrophil count, neutrophil-to-lymphocyte ratio, platelet count, hematocrit levels, hemoglobin levels), paraclinical examinations (tumor location, histological type), intraoperative findings (tumor location, size, tumor mobility/stiffness, local-regional extension, distant metastases, type of surgery), morphopathological examination (tumor size, macroscopic appearance, histological type, T stage - degree of bowel wall invasion, tumor grade (well-differentiated, undifferentiated), number of excised lymph nodes, N stage, number of examined lymph nodes, the relationship between the number of metastatic lymph nodes and the number of lymph nodes examined (defined as lymph node ratio - LNR), vascular invasion, perineural invasion, the presence of necrosis and its quantification, the quantification of mucinous component, peritumoral desmoplastic reaction and its quantification, peritumoral lymphocytic infiltration, resection margin invasion).

The following parameters were considered: white blood cell count divided into 3 categories (<8500/mm^3; 8500-11.000/mm^3; >11.000/mm^3) as indicated by Leitch et al. [6], lymphocyte count (<1000/mm^3; 1000-3000/mm^3; >3000/mm^3), neutrophil count (<7500/mm^3; >7500/mm^3), neutrophil-to-lymphocyte ratio (cut-off value = 5), hemoglobin levels (11.5-15 g/dl), hematocrit levels (37-47%), platelet count (150,000 to 370,000/mm^3) according to studies carried out by Sasaki et al. [7], the presence of anemia (<11 g/dl for men; <10 g/dl for women).

The degree of cell differentiation was assessed, resulting in four degrees of differentiation: G1- well differentiated, G2 - moderately differentiated, G3 - poorly differentiated, G4- undifferentiated. According to studies conducted by Petersen et al. [8], Petersen index was calculated using four morphopathological variables, each being assigned a score. Therefore, venous invasion, peritoneal damage and resection margin invasion were assigned a score of 1, and tumor perforation was assigned a score of 2. The total score was calculated by summing up these scores, resulting in an index with values between 0 and 5, further divided into low risk (0-1) and high risk [2-5]. Local inflammatory response was calculated using Klintrup [9], at the edge of the invaded tumor, quantifying the local inflammatory infiltrate. Score 0 is assigned in case of complete absence of inflammatory infiltrate at the edge of the invaded tumor. Score 1 is assigned to

a minimum or average infiltrate and score 2 to a prominent inflammatory infiltrate. A score of 3 as part of Klintrup criteria indicates an extremely rich inflammatory infiltrate which occasionally disrupts cellular architecture. Local inflammatory response is considered low for scores 0 and 1 and high for scores 3 and 4.

Tumor necrosis was also quantified, assigning score 0 for absence of necrosis, 1 for "focal" necrosis, less than 10%; 2 for "moderate" necrosis, between 10 and 30%; 3 for "extensive" necrosis, more than 30%, as indicated by Richards et al. [10]. Mucinous component was quantified, with a 0 score assigned in case of absence of mucinous component; 1 when mucinous component is minimal, less than 10%; 2 when mucinous component is moderate, between 10-50%, and 3 in case of an extensive mucinous component, over 50%.

Desmoplasia was assigned a score of 0 when absent, 1 when moderate or minimum, 2 for average and 3 for marked / important / extended desmoplasia [11-14].

For patients with stage III cancer, the lymph node ratio (LNR) was calculated by dividing the number of tumor invaded lymph nodes to the total number of resected lymph nodes. Based on this criterion, patients were divided into 5 groups, with the following cut-off values: <0.10, 0.11-0.21, 0.22-0.36, 0.37-0.6, and >0.61. This LNR classification had already been applied in several previous studies [11-14]. Also, in a subgroup of patients, the preoperative systemic/general inflammatory response was calculated using the modified Glasgow score (MGPs) and calculated according to C-reactive protein values and albumin levels. Thus, CRP <10 mg/l associated with albumin levels below or over 35 g/l is assigned score 0; CRP >10 mg/l associated with hypoalbuminemia <35 g/l is assigned score 2; CRP >10 mg/l associated with hyperalbuminemia >35 g/l is assigned score 1, according to the classification used by Richards et al. [15].

Patients were followed for a period of 5 years, after 3 and 6 months in the first year after surgery and annually in the coming years.

Statistical analysis was performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Quantitative data were tested for normality of distribution using Kolmogorov-Smirnov test. Quantitative variables were characterized as median and 25th and 75th percentiles (non-normal distribution). Nominal and ordinal variables were characterized as frequency and percentage. Differences between groups regarding quantitative variables were calculated using the Mann-Whitney test. Differences in the frequency of nominal or ordinal variables between the two groups were calculated using the Chi-square test or Fisher test, as appropriate. ROC curves were used in order to calculate cut-off values for continuous variables that discriminate between death and survival. The cut-off value was chosen were sensibility and specificity were maximum. The survival analysis was performed using Kaplan-Meier analysis and Cox regression. A p value of <0.05 was set as statistically significant threshold.

Results

After applying the exclusion criteria previously outlined, a total sample size of 301 patients was obtained. There were 197 patients (66.4%) who survived during the five-year follow-up period and 104 patients (34.6%) who died during this period.

Age of patients who survived [62 (55; 69) years] did not statistically significantly different from that of patients who died [62 (52; 69.7) years] (p=0.9). The main clinical and paraclinical characteristics of the study group are presented in Table I.

Of the patients with colon cancer, 54 (34%) had tumor located on the right side of the colon. Among these patients there were 21 (46.7%) deaths, a significantly higher frequency than in tumors with other locations (p=0.03). There were 16 (10.1%) patients with trans-

TABLE I - *The main clinical and paraclinical characteristics of the study group*

Variable	Survivors	Deceased	p
Age	62 (55; 69)	62 (52; 69.7)	0.9
Location	114 (57.9%)	45 (43.3%)	0.2
Colon	83 (42.1%)	59 (56.7%)	0.3
Rectum			
WBC count			
<8500/mm^3	151 (76.2%)	47(45.2%)	
8500-11000/mm^3	30 (15.2%)	34 (32.7%)	<0.001
>11000/mm^3	16(8.1%)	23 (22%)	
Neutrophil-to-lymphocyte ratiomedian	3.3 (1.5;6)	2.7(2.1;3.4)	<0.001
Hemoglobin (mg/dl)	12.5 (11.1;13.8) mg/dl	11.5 (10.4;13.2)mg/dl	0.003
Platelet count/mm^3	300000 (237500;369500)	269500 (230000;311500)	0.03

Table II - *The main morphopathological characteristics*

Variable	Survivors	Deceased	p
TNM			
I	36 (18.3%)	5 (4.8%)	
IIA	66 (33.5%)	15(14.4%)	
IIB	19 (9.6%)	11(10.6%)	
IIC	4 (2.0%)	5 (4.8%)	
IIIA	20 (10.2%)	5 (4.8%)	<0.001
IIIB	37 (18.8%)	35(33.7%)	
IIIC	15 (7.6%)	28(26.9%)	
Number of excised nodes	12 (10;14)	12 (11;15)	0.009
LNR1	35 (52.2%)	7 (10.6%)	
LNR2	13 (19.4%)	10 (15.2%)	
LNR3	9 (13.4%)	15(22.7%)	
LNR4	8 (11.9%)	20(30.3%)	<0.001
LNR5	2 (3%)	14 (21.2%)	
Tumor size			
< 4 cm	72 (36.5%)	34 (32.7%)	0.5
> 4 cm	125 (63.5%)	70 (67.3%)	
median	5 (4;7)	5 (4;6.3)	0.2
Tumor grade			
G1	66 (33.5%)	6 (5.8%)	
G2	124 (62.9%)	70(67.3%)	
G3	7 (3.6%)	24(23.1%)	<0.001
G4		4 (3.8%)	
Klintrup score			
low (0;1)	61 (30.9%)	95 (91.4%)	<0.001
high (3;4)	136 (69.1%)	9 (8.6%)	
Petersen score			
Low risk (0-1)	186 (94.4%)	52 (50%)	<0.001
High risk (2-5)	11(5.6%)	52 (50%)	
Venous invasion	14 (7.1%)	60 (57.7%)	<0.001
Perineural invasion	8 (4.1%)	24 (23.1%)	<0.001
Necrosis			
0	59 (29.9%)	14 (13.5%)	
1	78 (39.6%)	15(14.4%)	
2	37 (18.8%)	23 (22.1%)	<0.001
3	23 (11.7%)	52 (50%)	
Mucinous component			
0	160 (81.2%) 19(9.6%)	55 (52.9%)	
1	6 (3%)	8 (7.7%)	<0.001
2	12 (6.1%)	9 (8.7%)	
3		32 (30.8%)	
Desmoplasia			
0	29 (14.7%)	56 (53.8%)	
1	28 (14.2%)	20 (19.2%)	<0.001
2	58 (29.4%)	15 (14.4%)	
3	82 (41.6%)	13 (12.5%)	

verse colon cancer, of which four (8.9%) died. There were 87 (54.7%) patients with tumor on the left side of the colon, of which 19 (42.2%) died.

Of the patients with rectal cancer, 57 (40.1%) had low rectal cancer, of which 24 (40.7%) died. There was no difference in prognosis depending on rectal cancer location.

Anemia was more frequently associated with cancers occurring on the right side of the colon. Patients with anemia were more likely to die, 48 (46.2%) deceased vs. 63 (32%) survivors (p=0.01). The need for transfusion was associated with increased mortality rates (p=0.002).

Patients who died had median tumor size of 5 (4; 6.3) cm, and those who survived had median tumor size of 5 (4; 7) cm. The main morphopathological characteristics are summarized in Table II.

Survival rates depending on cancer stage were as follows: 87.8% for stage I, 81.5% for stage IIA, 63.33% for stage IIB, 44.4% for stage IIC. The following

Table III - *Multivariate Cox regression for survival*

Variable	B	P	HR	IC 95%	
				Min	Max
Age > 60 years	0.43	0.05	1.53	0.98	2.39
Males	0.54	0.01	1.73	1.10	2.70
WBC >8170/mm^3	0.37	0.1	1.45	0.85	2.47
Neutrophil-to-lymphocyte ratio >5	0.14	0.6	1.15	0.67	1.97
Anemia	-0.04	0.8	0.95	0.59	1.53
Thrombocytes >370000 mm^3	0.4	0.1	1.50	0.87	2.57
Colon	-0.54	0.02	0.57	0.35	0.94
Grading (2)	0.70	0.1	2.02	0.82	4.97
Grading (3)	0.74	0.1	2.09	0.75	5.83
Grading (4)	2.49	0.001	12.10	2.72	53.80
T >2	0.80	0.02	2.23	1.11	4.47
N >	0.35	0.1	1.43	0.89	2.28
Klintrup > 1	-1.59	<0.001	0.20	0.09	0.44
Venous invasion	0.81	0.003	2.26	1.31	3.91
Perineural invasion	-0.22	0.4	0.79	0.44	1.44
Necrosis score (1)	0.23	0.5	1.26	0.55	2.85
Necrosis score(2)	0.42	0.2	1.53	0.70	3.34
Necrosis score (3)	0.21	0.5	1.24	0.62	2.46
Desmoplasia score (1)	-0.10	0.7	0.90	0.48	1.66
Desmoplasia score (2)	-0.80	0.02	0.44	0.22	0.90
Desmoplasia score (3)	-0.86	0.01	0.42	0.20	0.85
Mucinous component score	0.07	0.7	1.07	0.64	1.79
Number of lymph nodes	-0.18	0.4	0.832	0.49	1.41

results were obtained for stage III: 80% for stage IIIA, 51.38% for stage IIIB, and 34.88% for stage IIIC.

The hazard ratio (HR) was 3.3 (95% CI 1.14 to 9.51) for patients with stage IIB cancer, compared with stage I patients (p=0.02). The HR was 5.2 (95% CI 1.5 to 18.08) for patients with stage IIC, compared with stage I patients (p=0.009). The HR was 4.9 (95% CI 1.9 to 12.6) for patients with stage IIIB cancer, compared with stage I patients (p=0.001). The HR was 7.8 (95% CI 3.03 to 20.43) for patients with stage IIIC cancer, compared with stage I patients (p<0.001).

There was a highly statistically significant difference in terms of survival in patients with T>2 (93 (89.4%)), compared with those with T=<2 (11 (10.6%) (p<0.001), as well as a highly statistically significant difference in the survival of patients with N>0 [67 (64.4%)], compared with those with N=0 (37 (35.6%)) (p<0.001). There was a statistically significantly greater survival rate for N1 group than for N2 group (p<0.001). The number of excised lymph nodes ranged from 6 to 29, with a median of 12 (10, 15). In deceased patients, the number of excised lymph nodes was 12 (11; 15), compared to 12 (10, 14) for survivors. The difference was statistically significant (p=0.009).

For patients with stage III cancer (N+) the LNR was 0.4 (0.21; 0.6) in deceased patients and 0.25 (0.1; 0.5) in survivors. Higher death rates were observed among patients with higher LNR (p<0.001).

The HR was 3.1 (95% CI 1.27 to 8.34) for patients with a LNR ranging from 0.11 to 0.21, compared to those with a LNR <0.1 (p=0.01). The HR was 5.4 (95% CI 2.2 to 13.2) for patients with a LNR ranging from 0.22 to 0.36, compared to those with LNR <0.1 (p<0.001). The HR was 6.7 (95% CI 2.8 to 16) for patients with a LNR ranging from 0.37 to 0.6, compared to those with LNR <0.1 (p<0.001). The HR was 12.3 (95% CI 4.9 to 31) for patients with a LNR >0.61, compared to those with a LNR <0.1 (p<0.001).

The association between the 5 LNR groups and N stage resulted in a p value of 0.007, which was statistically significant (Fisher's exact test), demonstrating that the LNR is associated with N stage. A high

Klintrup score was observed in 9 (8.7%) deceased patients, and in 136 (69%) survivors. This difference in survival was highly statistically significant (p<0.001).
A high Petersen Index score was determined and the difference was statistically significant (p<0.001) between the two groups.
Venous invasion revealed a highly statistically significant difference (p<0.001) and perineural invasion was observed in 32 patients, of which 8 (4.1%) survivors and 24 (23.1%) deceased. The difference was highly statistically significant (p<0.001).
Patients with higher necrosis scores had higher death rates. The difference was highly statistically significant (p<0.001). Patients with higher mucinous component scores had higher death rates. The difference was highly statistically significant (p<0.001). Patients with lower desmoplasia scores had higher death rates. The difference was highly statistically significant (p<0.001).
Several predictive models were built using Cox regression in order to determine the independent character of the parameters for establishing the prognosis after 5 years for patients with colorectal cancer who had radical surgery. The analysis included the variables which reached statistical significance in univariate analysis. In the end, the most stable model was chosen (Table III).
Univariate analysis showed that death rate was statistically significantly higher in patients with a larger number of leukocytes. When multivariate analysis was conducted, leukocytes lost their independent prognostic role. The value of 8,170 leukocytes/mm^3 was identified as cut-off value, with a specificity of 73.1% and a sensitivity of 60.58%.Univariate analysis indicated that a neutrophil-to-lymphocyte ratio over 5 (p <0.001) was associated with a decrease in survival. A ratio of 5 was identified as cut-off value, with a specificity of 64.29% and a sensitivity of 65.38%. When multivariate analysis was conducted, the neutrophil-to-lymphocyte ratio (>5) did not prove to be significant.
Age over 60 years was associated with a HR of 1.53 (95% CI 0.98-2.39) for deaths (p=0.05). Males were more frequently associated with deaths (HR - 1.73; 95% CI 1.10-2.70; p=0.01). The location in the colon was associated with a better survival than the location in the rectum (HR - 0.57; 95% CI 0.35-0.94; p=0.02). Patients with grade G4 had a poorer prognosis than those with grade G1 (HR - 12.1; 95% CI 2.72-53.80; p=0.001). Patients with T>2 had a poor prognosis compared to those with T=<2 (HR - 2.23; 95% CI 1.11-4.47; p=0.02). Patients with Klintrup score >1 had a better prognosis than those with Klintrup =<1 (HR - 0.20, 95% CI 0.09- 0.44; p<0.001). Patients with venous invasion had a worse prognosis than those without venous invasion (HR - 2.26; 95% CI 1.31-3.91; p=0.003). Patients with desmoplasia score 2 had lower death rates than those with score 1 (HR - 0.44; 95% CI 0.22-0.90; p=0.02). Patients with desmoplasia score 3 had lower death rates than those with score 1 (HR - 0.42; 95% CI 0.22-0.85; p=0.01). The other variables did not have an independent influence on the prognosis of five-year survival. (Table III).
The following Glasgow scores were obtained in patients where CRP levels could be determined: Glasgow score 0 for 24 (68.6%) deceased patients and 62 (80.5%) survivors; Glasgow score 1 for 2 (5.7%) deceased patients and 13 (16.9%) survivors; Glasgow score 2 for 9 (25.7%) deceased patients and 2 (2.6%) survivors. Patients with a higher Glasgow score had higher death rates (p<0.001).

Discussion

The results of the study showed that age over 60 was associated with more deaths, location of the tumor in the colon was associated with better survival, grade G4 had a poorer prognosis, Patients with T>2 had poorer prognostic, Klintrup score >1 reveal better prognosis, the presence of venous invasion shows worse prognosis and score 3 of desmoplasia reveal better survival.
The combination of C-reactive protein values and albumin concentration (mGPS) is associated with overall survival in patients undergoing curative surgery for colorectal cancer.
In our study, when univariate analysis was conducted, cellular components (and not only) which make up the general inflammatory system were statistically significantly associated (leukocytes, lymphocytes, neutrophils, neutrophil-to-lymphocyte ratio, platelet count, C-reactive protein, albumin levels, mGPS) with five-year survival, predicting poor prognosis, as demonstrated in other types of cancer [16].
The data obtained helped demonstrate that general inflammatory response components, determined prior to surgery, are associated with survival in patients undergoing surgery for colorectal cancer, being prognostic factors.
Overall 5-year survival was higher in patients with colon cancer, the difference being significant when both univariate and multivariate analyses were conducted, resulting that the location in the colon is an independent positive prognostic factor. Several studies consider that there is a relationship between tumor location and different molecular models involving different defense and progression mechanisms that determine different prognosis models, which would also require different treatment strategies [17-19].
The data in the present study indicate that 5-year survival is lower in patients with stage IIC (T4bN0) cancer and stage IIB (T4aN0) cancer than in those with stage IIIA (T1, T2N1) cancer, as shown in other studies [20,21]. This could be explained by the penetration to the surface of the peritoneum (T4a) and direct invasion of other organs or structures (T4b), when there is no distinction between the invasion of the pelvic wall and the invasion of visceral organs, although resectability and survival rates are different between the two cases, lower in the first, particularly in rectal cancer [22]. Therefore, some studies sug-

gest the reclassification of T4bN0 stage in colon cancer stage IIIA and in rectal cancer stage IIIB [20]. Secondly, patients with stage III cancer receive adjuvant chemotherapy, unlike patients with stage II cancer. Thus, it is very important to identify other prognostic factors, besides TNM classification, which would divide patients into risk groups that could benefit from new therapeutic options.

According to various studies [23-25], patients divided according to N stage based on the absolute number of positive lymph nodes are not consistently distributed, hence the usefulness of the lymph node ratio (LNR).

Patients in our study were divided into five groups (1-5) depending on LNR intervals, showing a statistically significant proportional relationship between five-year survival rates and the five LNR groups. These data demonstrate that the use of LNR together with TNM staging can provide a better prediction.

Our results indicated the association between Klintrup score and overall survival when both univariate and multivariate analyses were conducted, indicating itself as an independent prognostic factor in accordance with other studies that examined this score as a prognostic factor [26-28].

In our study, Petersen score [8] was highly significantly associated with five-year survival when univariate analysis was conducted (p<0,001).

For the first time in the literature, mucinous component score was used in this formula in the present study. Mucinous component score was statistically significantly associated with 5-year overall survival when univariate analysis was conducted (p<0.001), considered to be a poor prognostic factor.

Desmoplasia score was also first used in this formula in the present study. In our study, patients with lower desmoplasia scores had higher death rates. Desmoplasia score 3 was found statistically significant when multivariate analysis was conducted, proving to be a positive prognostic factor, independent of other prognostic factors.

Five-year survival was superior for patients with colon cancer, and the location within the colon itself was a positive independent prognostic factor. The data obtained helped demonstrate the important role of the systemic inflammatory response of the host to tumour aggression and its prognostic implications in survival. Problems and limitations of the TNM classification were identified, which explains the need to find new prognostic factors that can be used individually or in association with the existing TNM classification in order to identify subgroups of patients at risk that could be monitored closely and would require individualized treatment.

The calculation of the LNR provides better prediction than the calculation of the number of positive lymph nodes and, when used in association with TNM staging, LNR can be an independent prognostic factor. Mucinous component score and desmoplasia score, first used in this formula in this study, can be used as positive independent prognostic factors in survival.

Conclusion

We identified the following new prognostic factors in colorectal cancer: desmoplasia and mucinous component. Also, other prominent factors validated the prognostic role: age, tumor location, stage T> 2, LNR, Klintrup score, Glasgow score. These prognostic factors and scores combined with TNM staging can improve the prediction of survival in these patients and should be included in the routine paraclinical and histopathological examination.

Riassunto

Scopo finalizzato all'analisi e valutazione dei fattori prognostici per la sopravvivenza in pazienti sottoposti a chirurgia curativa per cancro del colon-retto e per identificare nuovi fattori prognostici.

Si tratta di uno studio prospettico comprendente 301 pazienti con diagnosi di cancro del colon-retto, stadio I-III, sottoposti a chirurgia curativa e seguiti per cinque anni dopo l'intervento chirurgico.

Sono stati registrati dati demografici, dati clinici e anamnestici, esami di laboratorio, esami paraclinici, esame morfologico e patologico, ed è stato calcolato l'indice di Petersen.

Sono stati presi in considerazione necrosi tumorale, desmoplasia e componente mucinosa sull'istologia. La risposta infiammatoria locale è stata calcolata usando i criteri di Klintrup.

Al follow-up di 5 anni i pazienti sopravvissuti sono stati 197 pazienti (66,4%) e quelli deceduti 104 pazienti (34,6%). L'analisi multivariata ha mostrato che la morte è risultata associata principalmente a pazienti di età superiore a 60 anni (p = 0,05). La sopravvivenza è risultata migliore in caso di posizione del tumore all'interno del colon rispetto alla localizzazione del tumore all'interno del retto (HR - 0,57; p = 0,02). I pazienti con T> 2 hanno avuto una prognosi sfavorevole rispetto a quelli con T = <2 (HR - 2,23; p = 0,02). I pazienti con punteggio Klintrup> 1 hanno presentato una prognosi migliore (HR - 0.20; p <0.001); quelli con invasione venosa hanno mostrato prognosi significativamente peggiore (HR - 2,26; p = 0,003), e quelli con punteggio di desmoplasia 3 hanno avuto tassi di mortalità inferiori rispetto a quelli con punteggio 1 (HR - 0,42; p = 0,01).

In conclusione la sopravvivenza è risultata superiore nei pazienti con cancro del colon rispetto a quelli con cancro del retto. I seguenti parametri avevano un forte fattore prognostico indipendente per la sopravvivenza: età, stadio T> 2, invasione venosa, componente mucinosa e desmoplasia.

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