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Research Article

Assessment of clinical and pathological prognostic factors for colorectal cancer recurrence after surgery

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Abstract. Aim: to assess and analyse the prognostic factors for survival in patients who had been previously subjected to curative surgery for colorectal cancer. Moreover, the aim was to identify and consider new prognostic factors in colorectal cancer, to assess the prognostic role of local and systemic inflammatory response, as well as the prognostic role of lymph node ratio (LNR) in stage III colorectal cancer subjected to radical surgery. Material and methods: patients diagnosed with stage I-III colorectal cancer, admitted and undergoing radical surgery within the 5th Surgical Clinic of Cluj-Napoca Municipal Hospital between January 1999 and December 2008 were included in the study. A database was created, including demographic data, clinical and anamnestic data, laboratory exams, paraclinical examinations, intraoperative findings, morphopathological examination. The Petersen index was calculated using four morphopathological variables, each being assigned a score. Local inflammatory response was calculated using Klintrup criteria. For patients with stage III cancer, the lymph node ratio (LNR) was calculated by dividing the number of tumour invaded lymph nodes to the total number of resected lymph nodes. Results: there were 112 (37.2%) patients in the study experiencing cancer recurrence during the 5-year follow-up, and 189 (62.8%) patients who did not develop recurrence. Patients with grade 4 cancer had a higher likelihood of cancer recurrence than those with grade 1 cancer (HR-13.4; 95%CI=3.15-61.62; p=0.001). Patients with stage IIIB cancer were more likely to develop recurrences than those with stage I cancer (HR-7.22; 95%CI=0.92-56.26; p=0.05). Patients with stage IIIC cancer were more likely to develop recurrences than those with stage I cancer (HR - 9.75; 95% CI 1.23-77.35; p=0.03). Patients with Kintrup score >1 had a better prognosis than those with Klintrup ≤1 (HR-0.10; 95%CI=0.04-0.25; p<0.001). Patients with Petersen score >1 had a worse prognosis than those without venous invasion (HR-1.92; 95%CI=1.17-3.61; p=0.01). Patients with necrosis score 2 had a poorer prognosis than those with score 0 (HR-2.84; 95%CI=1.31-6.16; p=0.008). Patients with desmoplasic score 3 had lower recurrence rates than those with score 1 (HR-0.43, 95%CI=0.22-0.95; p=0.01). The other variables did not have an independent influence on the prognosis of five-year survival. Conclusion: cancer recurrences were more frequent in patients with tumour grade 4, stage IIIB or IIIC. The independent prognostic role of Klintrup and Petersen scores in cancer recurrences was also demonstrated. Desmoplasia score was an independent and positive prognostic factor for 5-year recurrence in patients with colorectal cancer who had curative surgery.

Key Words: colorectal cancer, recurrence, prognostic factors.

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Introduction

Colorectal cancer is still a leading cause of death in developed countries and there has been no significant improvement in the 5-year survival rate (van de Velde et al 2013). Prognostic factors should always be considered before therapy planning for colorectal cancer.

Although the AJCC/UICC TNM staging system (Stephen et al 2010) is currently the most powerful prognostic parameter in patients with colorectal cancer, new histopathological prognostic factors are needed in order to improve clinical decisions regarding postoperative follow-up and the management of adjuvant therapy.

Despite radical treatment, many patients experience local and/or distant recurrences. These high-risk patients require a more aggressive treatment or a more careful postoperative follow-up in order to improve prognosis. Therefore, the development of new therapeutic techniques should also be accompanied by a preoperative staging system classifying patients according to the risk of cancer recurrence and survival rates.

Although therapeutic procedures are well established and they are equally applied to all patients, the results in terms of survival and cancer recurrence incidence vary, probably due to the impact of certain prognostic factors that depend on both individual and tumour characteristics.

Based on existing data in the literature, the aim of the present study was to assess and analyse the prognostic factors for survival in patients who had been previously subjected to curative surgery for colorectal cancer. Moreover, the aim was to identify

and consider new prognostic factors in colorectal cancer, to assess the prognostic role of local and systemic inflammatory response, as well as the prognostic role of lymph node ratio (LNR) in stage III colorectal cancer subjected to radical surgery.

Materials and methods

In order to achieve these objectives, patients diagnosed with stage I-III colorectal cancer, admitted and undergoing radical surgery within the 5th Surgical Clinic of Cluj-Napoca Municipal Hospital between January 1999 and December 2008 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.

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, haemoglobin levels), paraclinical examinations (tumour location, histological type) intraoperative findings (tumour location, size, tumour mobility/stiffness, local-regional extension, distant metastases, type of surgery), morphopathological examination (tumour size, macroscopic appearance, histological type, T stage - degree of bowel wall invasion, tumour 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, lymphatic vessel invasion, perineural invasion, the presence of necrosis and its quantification, the quantification of the mucinous component, peritumoral desmoplasic reaction and its quantification, peritumoral lymphocytic infiltration, resection margin invasion).

The following parameters were considered: white blood cell count divided into 3 categories as indicated by Leitch (Leitch et al 2007)(<8,500/mm^3; 8,500-11,000/mm^3; >11,000/mm^3), lymphocyte count (<1,000/mm^3; 1,000-3,000/mm^3; >3,000/mm^3), neutrophil count (<7,500/mm^3; >7,500/mm^3), neutrophil-to-lymphocyte ratio (cut-off value = 5), haemoglobin 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 (Sasaki et al 2012), the presence of anemia (<11 g/dL for men, <10 g/dL for women).

A new anatomopathological microscopic analysis was conducted assessing tumour invasion margin and redefining the TNM cancer staging system according to the latest edition of the AJCC Cancer Staging Manual (the seventh), effective on or after 1 January, 2010 (Stephen et al 2010).

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 (Petersen et al 2002), Petersen index was calculated using four morphopathological variables, each being assigned a score. Intramural and extramural venous invasion, peritoneal damage and resection margin invasion were assigned a score of 1, tumour perforation was assigned a score of 2. The total score was calculated by summing up these scores, resulting in Petersen index with values between 0 and 5, divided into low risk (0-1) and high risk (2-5).

Local inflammatory response was calculated using Klintrup criteria (Klintrup et al 2005), at the edge of the invaded tumour, quantifying the local inflammatory infiltrate. Score 0 is assigned in case of complete absence of inflammatory infiltrate at the edge of the invaded tumour. Score 1 is assigned to a minimum or average infiltrate and a 2 score 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.

Tumour 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 (Richards et al 2012).

Mucinosa was another component being quantified, with a 0 score assigned in case of absence of the mucinous component; 1 when the mucinous component is minimal, less than 10%; 2 when the 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.

For patients with stage III cancer, the lymph node ratio (LNR) was calculated by dividing the number of tumour 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, 0.1-0.21, 0.22-0.36, 0.37-0.6 and >0.61. This LNR classification had already been applied in several previous studies (Vaccaro et al 2009; Chen et al 2011; Kelly et al 2013; Micu et al 2013).

Patients with stage I-II cancer did not receive neoadjuvant therapy after surgery and most patients with stage III cancer received chemotherapy with 5-fluorouracil.

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, through complete clinical examination, laboratory tests, chest X-ray, abdominal ultrasound, colonoscopy and CT for screening purposes.

Distant recurrences were identified by general local exam and paraclinical examination (laboratory tests, chest X-ray, general ultrasound, computed tomography, scintigraphy), while local recurrences were detected by abdominal ultrasound and/or lower gastrointestinal endoscopy with anastomotic biopsy. The period (number of months) following surgery until the occurrence of

local-regional or distant recurrences was calculated and defined as relapse-free survival.

Statistical analysis was performed using MedCalc version 14.8.1. Data were presented as median and 25th and 75th percentiles (non-normal distribution - Kolmogorov Smirnov test) or as frequency and percentage, depending on the situation. The comparison between the two groups was performed using the Mann-Whitney test or the chi-square test, depending on the situation. Univariate analysis of recurrence was performed using the log-rank test. Multivariate analysis of prognostic factors for cancer recurrence was performed using Cox regression model.

Results

There were 112 (37.2%) patients in the study experiencing cancer recurrence during the 5-year follow-up, and 189 (62.8%) patients who did not develop recurrence.

Age of patients with cancer recurrence (60 (50; 68) years) did not differ significantly from that of those without recurrence (64 (55; 70 years) (p=0.08). There were 46 (41 1%) women and 66 (58.9%) men in the group of patients who experienced cancer recurrence, and 88 (46.6%) women and 101 (53.4%) men in the group of patients without cancer recurrence. The difference in gender distribution in the two groups was not statistically significant (p=0.4).

There were 41 (36.6%) patients who had abdominal pain on admission in the group of patients who experienced cancer recurrence, and 69 (36.5%) patients with the same symptom in the group of patients without cancer recurrence. The difference in the distribution of pain in the two groups was not statistically significant (p=1). There were 29 (25.9%) patients with rectal bleeding on admission in the group of patients who experienced cancer recurrence, and 45 (23.8%) patients with the same symptom in the group of patients without cancer recurrence. The difference in rectal bleeding distribution in the two groups was not statistically significant (p=0.7). There were 10 (9.6%) patients who experienced rectal tenesmus on admission in the group of patients who experienced cancer recurrence, and 10 (5.3%) patients with the same symptom in the group of patients without cancer recurrence. The difference in rectal tenesmus distribution in the two groups was not statistically significant (p=0.2). There were 32 (29.4%) patients with abnormal bowel transit on admission in the group of patients who experienced cancer recurrence, and 62 (32.8%) patients with the same symptom in the group of patients without cancer recurrence. The difference in the distribution of bowel transit disorders in the two groups was not statistically significant (p=0.6).

The number of leukocytes in patients who experienced cancer recurrence was statistically significantly higher (8,600 (6,800; 11,000/mm³) than in the group of patients without cancer recurrence 7,100 (6,200; 8,375/mm³) (p<0.001). In patients who experienced cancer recurrence, leukocyte count was <8,500/mm³ in 54 (48.2%) cases, between 8,500/mm³ and 11,000/mm³ in 33 (29.5%) cases, and >11,000/mm³ in 25 (22%) cases. In patients without cancer recurrence, leukocyte count was <8,500/mm³ in 144 (76.2%) cases, between 8,500/mm³ and 11,000/mm³ in 31 (16.4%) cases, and >11,000/mm³ in 14 (7.4%) cases. Cancer recurrence rate was statistically significantly higher in patients with higher levels of leukocytes (p<0.001).

The number of neutrophils in patients who experienced cancer recurrence was statistically significantly higher (6,450 (4,925; 8,475/mm³) than in patients without cancer recurrence (5,200 (4,078; 6,700/mm³) (p<0.001). Neutrophil count was >7,500/mm³ in 39 (34.8%) patients who experienced cancer recurrence and in 25 (13.2%) patients without cancer recurrence. Cancer recurrence rate was statistically significantly higher in patients with higher levels of neutrophils (p<0.001).

The number of lymphocytes in patients who experienced cancer recurrence was statistically significantly lower (1,690 (1,200; 2,100/mm³) than in patients without cancer recurrence (1,855 (1,500; 2,357/mm³) (p=0.005). Patients who experienced cancer recurrence had a lymphocyte count of <1,000/mm³ in 15 (13.4%) cases, between 1,000/mm³ and 3,000/mm³ in 91 (81.2%) cases, and >3,000/mm³ in 6 (5.4%) cases. Patients without cancer recurrence had a lymphocyte count of <1,000/mm³ in 8 (4.2%) cases, between 1,000/mm³ and 3,000/mm³ in 163 (86.2%) cases, and >3,000/mm³ in 18 (9.5%) cases. Cancer recurrence rate was significantly different depending on the group (p=0.01).

Neutrophil-to-lymphocyte ratio (NLR) was statistically significantly higher in patients who experienced cancer recurrence (3.4 (2.6, 5.9) than in those without cancer recurrence (2.6 (2.1, 3.4) (p<0.001). Neutrophil-to-lymphocyte ratio (NLR) was >5 in 42 (37.5%) patients who experienced cancer recurrence and in 18 (9.5%) patients without cancer recurrence. The difference in cancer recurrence rate depending on neutrophil-to-lymphocyte ratio was of high statistical significance (p<0.001).

Hemoglobin levels were statistically significantly lower in patients who experienced cancer recurrence (11.8 mg/dL (10.5; 13.4)) than in those without cancer recurrence (12.4 mg/dl (11; 13.7)) (p=0.02). Hematocrit levels were statistically significantly lower in patients who experienced cancer recurrence (37% (32; 41)) than in those without cancer recurrence (39% (34.4; 41.7)) (p=0.09). Patients with anemia were more likely to experience cancer recurrence (50 (44.6%) patients who experienced cancer recurrence vs. 61 (32.3%) patients without cancer recurrence) (p=0.01).

Platelet count was statistically significantly higher (300,000/mm³ (240,000; 360,000)) in patients who experienced cancer recurrence than in those without cancer recurrence (264,500/mm³ (230,000; 306,250)) (p=0.005). Platelet count was >370,000/mm³ in 21 (18.8%) patients who experienced cancer recurrence and in 20 (10.6%) patients without cancer recurrence. Cancer recurrence rate was statistically significantly higher in patients who had a platelet count of >370,000/mm³ (p=0.01).

Among patients who experienced cancer recurrence, 66 (58.9%) had rectal cancer and 46 (41.1%) had colon cancer. Of the patients without cancer recurrence, 76 (40.2%) had rectal cancer and 113 (59.8%) had colon cancer. Patients with rectal cancer were more likely to experience cancer recurrence (p<0.001).

Patients who experienced cancer recurrence had an average tumour size of 5 (4; 7) cm and those who survived had an average tumour size of 5 (4, 6.3) cm. There were no differences in tumour size between the two groups (p=0.3). Tumours larger than 4 cm were found in 73 (65.2%) of the patients who died and in 122 (64.6%) patients without cancer recurrence. The differences were not statistically significant (p=1).

Tumour grade 1 was present in 7 (6.2%) patients who experienced cancer recurrences and in 65 (34.4%) patients without

cancer recurrence. Tumour grade 2 was present in 76 (67.9%) patients who experienced cancer recurrence and in 118 (62.4%) patients without cancer recurrence. Tumour grade 3 was present in 25 (22.3%) patients who experienced cancer recurrences and in 6 (3.2%) patients without cancer recurrence. Tumour grade 4 was present in 4 (3.6%) patients who experienced cancer recurrences and none of the relapse-free patients. Survival rates differed depending on tumour grade (p<0.001).

Administration of blood transfusion was present in 92 (30.6%) patients, of whom 44 (39.3%) experienced cancer recurrences. The need for transfusion was associated with a higher recurrence rate (p=0.005).

TNM classification for the two groups can be seen in Table 1. There was a highly statistically significant difference in cancer stage in terms of survival (p<0.001).

Table 1. TNM stage distribution in the two groups

Stage		Group	
		Without recurrence	With recurrence
I	No.	40	1
	%	21.2%	0.9%
IIA	No.	66	15
	%	34.9%	13.4%
IIB	No.	18	12
	%	9.5%	10.7%
IIC	No.	4	5
	%	2.1%	4.5%
IIIA	No.	20	5
	%	10.6%	4.5%
IIIB	No.	32	40
	%	16.9%	35.7%
IIIC	No.	9	34
	%	4.8%	30.4%

A high Klintrup score was observed in 7 (6.2%) patients in the group who experienced cancer recurrence and in 138 (73%) patients without cancer recurrence. This difference was highly statistically significant (p<0.001).

A high Petersen Index score was determined in 58 (51.8%) patients in the recurrence group and in 5 (2.6%) patients without cancer recurrence. This difference was highly statistically significant (p<0.001).

Venous invasion was described in 7 (3.7%) patients without cancer recurrence and in 67 (59.8%) patients who experienced cancer recurrence. The difference was highly statistically significant (p<0.001).

Perineural invasion was described in 2 (1.1%) patients without cancer recurrence and in 30 (26.8%) patients who experienced cancer recurrence. The difference was highly statistically significant (p<0.001).

The distribution of necrosis score in the two groups can be seen in Table 2 . Patients with a higher necrosis score had higher recurrence rates. This difference was highly statistically significant (p<0.001).

Table 2. Necrosis score distribution in the two groups

Necrosis score		Group	
		Without recurrence	With recurrence
0	No.	61	12
	%	32.3%	10.7%
1	No.	74	19
	%	39.2%	17.0%
2	No.	36	24
	%	19.0%	21.4%
3	No.	18	57
	%	9.5%	50.9%

The distribution of the mucinous component score in the two groups can be seen in Table 3. Patients with a higher mucinous component score had higher recurrence rates. This difference was highly statistically significant (p<0.001).

Table 3. Mucinous component score distribution in the two groups

Mucinous component score		Group	
		Without recurrence	With recurrence
0	No.	154	61
	%	81.5%	54.5%
1	No.	17	10
	%	9.0%	8.9%
2	No.	7	8
	%	3.7%	7.1%
3	No.	11	33
	%	5.8%	29.5%

The distribution of desmoplasia score in the two groups can be seen in Table 4. Patients with a higher desmoplasia score had lower recurrence rates. This difference was highly statistically significant (p<0.001).

Table 4. Desmoplasia score distribution in the two groups

Desmoplasia score		Group	
		Without recurrence	With recurrence
0	No.	25	60
	%	13.2%	53.6%
1	No.	29	19
	%	15.3%	17.0%
2	No.	57	16
	%	30.2%	14.3%
3	No.	78	17
	%	41.3%	15.2%

Lymph node ratio (the relationship between the number of resected/examined lymph nodes) was 12 (10; 14) in patients who experienced cancer recurrence and 12 (11; 14.5) in patients without cancer recurrence. The difference was statistically significant (p=0.01).

Table 5. Multivariate Cox regression for cancer recurrence

Variable	B	Wald	P	HR	CI 95%	
					Min	Max
Age > 60 years	0.22	0.95	0.3	1.24	0.8	1.94
Leukocytes>8170/mm^3	0.34	1.45	0.2	1.4	0.8	2.45
NLR >5	-0.03	0.01	0.8	0.96	0.58	1.61
Anemia	-0.01	0	0.9	0.98	0.62	1.55
Thrombocytes >370000 mm^3	-0.04	0.03	0.8	0.95	0.56	1.62
Colon	-0.42	3.08	0.07	0.65	0.4	1.05
Grading (1)	0.65	2.26	0.1	1.92	0.81	4.53
Grading (2)	0.48	0.94	0.3	1.62	0.61	4.3
Grading (3)	2.63	12.07	0.001	13.94	3.15	61.62
TNM stage IIA	1.58	2.25	0.1	4.86	0.61	380.26
TNM stage IIB	1.7	2.48	0.1	5.47	0.66	45.37
TNM stage IIC	1.84	2.61	0.1	6.35	0.67	59.68
TNM stage IIIA	0.72	0.4	0.5	2.06	0.21	19.58
TNM stage IIIB	1.97	3.56	0.05	7.22	0.92	56.26
TNM stage IIIC	2.27	4.64	0.03	9.75	1.23	77.35
Klintrup score > 1	-2.22	26.89	<0.001	0.1	0.04	0.25
Petersen score >1	0.65	6.66	0.01	1.92	1.17	3.16
Perineural invasion	0.35	1.47	0.2	1.42	0.8	2.51
Necrosis score (1)	0.81	4.01	0.04	2.24	1.01	4.96
Necrosis score (2)	1.04	7.05	0.008	2.84	1.31	6.16
Necrosis score (3)	0.62	2.96	0.08	1.85	0.91	3.76
Mucinous component score >1	-0.36	1.45	0.2	0.69	0.37	1.26
Desmoplasia score (1)	-0.17	0.33	0.5	0.84	0.46	1.52
Desmoplasia score (2)	-1.05	8.25	0.004	0.35	0.17	0.71
Desmoplasia score (3)	-0.83	5.75	0.01	0.43	0.22	0.85
Lymph node ratio	0.01	0.31	0.5	1.01	0.95	1.07

Several predictive models were built using Cox regression in order to determine the independent character of the parameters for the prognosis of cancer recurrence 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 5). Patients with grade 4 cancer had a higher likelihood of cancer recurrence than those with grade 1 cancer (HR-13.4; 95%CI=3.15-61.62; p=0.001). Patients with stage IIIB cancer were more likely to develop recurrences than those with stage I cancer (HR-7.22; 95%CI=0.92-56.26; p=0.05). Patients with stage IIIC cancer were more likely to develop recurrences than those with stage I cancer (HR - 9.75; 95% CI 1.23-77.35; p=0.03). Patients with Kintrup score >1 had a better prognosis than those with Klintrup ≤1 (HR-0.10; 95%CI=0.04-0.25; p<0.001). Patients with Petersen score >1 had a worse prognosis than those without venous invasion (HR-1.92; 95%CI=1.17-3.61; p=0.01). Patients with necrosis score 1 had a poorer prognosis than those with score 0 (HR-2.24; 95%CI=1.01-4.96; p=0.04). Patients with necrosis score 2 had a poorer prognosis than those with score 0 (HR-2.84; 95%CI=1.31-6.16; p=0.008). Patients with desmoplasic score 2 had lower recurrence rates than those with score 1 (HR-0.35; 95%CI=0.17-0.71; p=0.004). Patients with desmoplasic score 3 had lower recurrence rates than those with score 1 (HR-0.43, 95%CI=0.22-0.95; p=0.01). The other variables did not have an independent influence on the prognosis of five-year survival.

For patients with stage III cancer, a LNR of 0.4 (0.21; 0.58) was calculated for patients who experienced cancer recurrence, and a LNR of 0.09 (0.07; 0.16) was obtained in those without cancer recurrence. Patients with higher LNR had higher recurrence rates (p<0.001).

A HR of 3.1 (95%CI=1.27-7.89) was obtained for patients in the LNR 0.11-0.21 category, compared to those in the LNR <0.1 category (p=0.01). A HR of 5.6 (95%CI=2.4-13.2) was obtained for patients in the LNR 0.22-0.36 category, compared to those in the LNR <0.1 category (p<0.001). A HR of 8.9 (95%CI=4-19.9) was obtained for patients in the LNR 0.37-0.6 category, compared to those in the LNR <0.1 category (p<0.001). A HR of 15 (95%CI=6.23-36.3) was obtained for patients in the LNR >0.61 category, compared to those in the LNR <0.1 category (p<0.001).

The following Glasgow scores were obtained in patients where CRP levels could be determined: Glasgow score 0 for 29 (69%)

patients who experienced cancer recurrence and 57 (81.4%) patients without cancer recurrence; Glasgow score 1 for 2 (4.8%) patients who experienced cancer recurrence and 13 (18.6%) patients without cancer recurrence; Glasgow score 2 for 11 (26.2%) patients who experienced cancer recurrence and no patient without cancer recurrence. Patients with a higher Glasgow score had higher recurrence rates ($p<0.001$).

Discussions

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 cancer recurrences, predicting poor prognosis, as demonstrated in other types of cancer (McMillan et al 2007).

The data obtained helped demonstrate the important role of the systemic inflammatory response of the host to tumour aggression, resulting from the interaction between the immune system and/or the inflammatory system of the host and the tumour (Colotta et al 2009). The outcome provides a better understanding of the relationships between the systemic inflammatory response and survival in patients with colorectal cancer who had undergone curative surgery. One explanation could be that tumour cells and those of the immune and vascular system contribute to the release and expression of proinflammatory cytokines, thus resulting in a close relationship between inflammation and cancer (Leitch et al 2007).

In the subgroup of patients with a change in the Glasgow score (calculated according to the levels of C-reactive protein and albumin levels) (Roxburgh et al 2009), which quantifies the systemic inflammatory response, a higher value of the score was statistically significantly associated with a higher recurrence rate when both univariate and multivariate analyses were conducted. More frequently, but without statistical significance, a high mGPS score was associated with distant recurrences. Therefore, it is an independent prognostic factor in identifying patients with increased risk for cancer recurrences.

The degree of differentiation has statistically significantly influenced the disease-free interval, grade G4 being significantly associated with cancer recurrence, thus being considered as an independent factor for recurrence.

There is an increased number of cases located in the rectum, observed also in other studies (Lese at al 2013). Cancers located within the rectum were associated with a high frequency of recurrences ($p<0.001$).

The analysis of cancer recurrence based on stages indicated a highly significant difference when univariate analysis was conducted ($p<0.001$). The risk of recurrence increased together with the stage. In the present study, the risk of recurrence in stages IIB and IIC was higher than in stage IIIA, especially in the case of local recurrences. This could be explained by the penetration to the surface of the visceral peritoneum (T4a) and direct invasion of other organs or structures (T4b). Therefore, some studies suggest the reclassification of T4bN0 stage in colon cancer stage IIIA and in rectal cancer stage IIIB (Li et al 2014). 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.

The frequency of cancer recurrences increases with the number of nodes invaded and it also increases the frequency of distant tumour recurrence. The distribution of cancer recurrence based on N1 and N2 is not uniform, but the introduction of LNR provides better prediction. However, no prediction can be made about the type of recurrence, as LNR did not differ significantly between patients with local recurrence and those with distant recurrence. Previous studies (Rosenberg et al 2008;Ceelen et al 2010) used different intervals to define LNR, using it only as a prognostic factor with a role in overall survival and cancer-specific survival. There are few studies using LNR as a prognostic factor for cancer recurrence, and results were uncertain. Using the hazard ratio, the present study demonstrated that there is a 9-fold increase in the risk of cancer recurrence between LNR<0.1 and LNR 0.36-0.6, respectively a 15-fold increase between LNR<0.1 and LNR>0.6.

Klintrup score statistically significantly influenced the disease-free interval when both univariate and multivariate analyses were conducted ($p<0.001$), indicating itself as an independent parameter. A low Klintrup score was associated with a high risk of recurrence, but it did not differ significantly between local and distant recurrences. Klintrup score accounts for local inflammatory response at the invading tumour edge. An important local inflammatory response generated by the host may prevent the infiltration of the invading tumour edge (Roxburgh et al 2009) and thus prevent the occurrence of tumour cell dissemination.

Petersen score was an independent prognostic factor for cancer recurrence when both univariate and multivariate analyses were conducted, unlike other studies that have only shown its prognostic role in survival (Petersen et al 2002, Morris et al 2007; Roxburgh et al 2009).

Patients with a high necrosis score had a higher rate of cancer recurrence. Therefore, necrosis score 3 determines a 2.84-fold increase in recurrence rate, compared to necrosis score 0. Necrosis score proved itself as an independent prognostic factor for the 5-year recurrence, confirming the findings of Guthrie et al (2013) demonstrating that there are strong connections between tumour necrosis and local and systemic inflammatory response, as necrosis causes the increase in circulating interleukin-6 levels and vascular endothelial growth factor levels, thereby modulating the local and systemic inflammatory response which will result in tumour progression and distant dissemination.

For the first time in the literature, desmoplasia score was used in this formula in the present study. Existing studies (Coulson-Thomas et al 2011; Ganggaiswari et al 2010) in the literature refer to the prognostic role of desmoplasia in overall survival with uncertain results, without determining the prognostic impact on recurrences. In our study, desmoplasia score proved to be an independent prognostic factor for cancer recurrences. Patients with higher desmoplasia scores had lower recurrence rates. Desmoplasia score 3 causes a 0.5-fold decrease in recurrence rate.

Conclusions

Cancer recurrences were more frequent when tumours were located within the rectum. Tumour grade G4 was statistically significantly associated with the occurrence of recurrent cancers,

demonstrating its independent role as a prognostic factor. Stages IIIB or IIIC are independent prognostic factors for cancer recurrence, especially for distant recurrences. The calculation of the NLR)provides better prediction of recurrences. The independent prognostic role of Klintrup and Petersen scores in cancer recurrences was also demonstrated. Patients with high necrosis scores had higher recurrence rates, demonstrating that necrosis score is an independent prognostic factor for cancer recurrences. Desmoplasia score, first used in this manner in the present study, can be used as an independent and positive prognostic factor for 5-year recurrence in patients with colorectal cancer who had curative surgery. In our study, patients with higher desmoplasia scores had lower recurrence rates.

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