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ORIGINAL ARTICLE

Localization, clinical and pathological characteristics and survival in sporadic colon cancer patients younger than 40 and over 65 years of age

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Summary

Purpose: *Colorectal cancer is predominantly a disease of older population, but occasionally it affects younger patients, in whom very often diagnosis is overseen and treatment begins late. The aim of our study was to compare localization, clinical and pathological characteristics and survival of sporadic colorectal cancer patients aged up to 40 and over 65 years.*

Patients and methods: *The first group (group I) included 19 patients under 40 years and the second group (group II) 28 patients aged over 65 years, treated during 1997-2001. Patients with family history of colon cancer and inflammatory disease of the colon were not included. Arithmetic mean, standard deviation, Fisher's test, Student's t test, x^2 test and the Kaplan-Meier method were used in the statistical analysis of the results.*

Results: *There was no difference among the tested groups regarding tumor localization. The most frequent localization was in the rectum and left colon. At presentation, in group I patients, besides the metastases in the liver and lymph nodes, colorectal cancer infiltrated also the duodenum, stomach, right kidney capsule in one patient, and adnexa in two patients. In group II patients we registered only liver and lymph node metastases. Pathologically, tubular and mucinous forms were present in all of the patients up to 40 years of age, while only one patient over 65 had tumor with mucinous component. In group I, Astler-Coller stage B was found in 1.5% of the patients, stage C in 72.5% and stage D in 26%; in group II, stage B was found in 1.5%, stage C in 84.5% and stage D in 14%. Grade III was 36.8% in group I and 17.8% in group II. No statistical differences were found in stage distribution (p=0.36) and grade (p=0.06) between group I and II. Five-year overall survival was 57.8% and 28.5% in younger and older patients, respectively (p=0.053).*

Conclusion: *The results obtained showed no difference in clinical symptomatology and tumor localization in both groups. The incidence of more aggressive tumors was higher in younger persons. However, early detection combined with more aggressive therapeutic approach, could enable significant improvement of the 5-year survival of younger patients with colon cancer.*

Key words: age, colon cancer, colonoscopy, survival, tumor localization

Introduction

Colorectal cancer is one of the most common types of cancer with 678,000 new cases and over 400,000 deaths all over the world per year, and ranks second as a cause of cancer death in Europe [1]. Sporadic colorectal cancer is rising gradually and it is a predominant disease in older population with a median age of 70 years at diagnosis. This type of cancer, together with prostate cancer, is the most common malignancy in male population aged over 65 years, with a cumulative risk less than 5% [2].

Sporadic colorectal cancer ranks second in women of the same age, with a cumulative risk of less than 3% [2]. Sporadic colorectal cancer without clearly predisposing factors also develops in persons under 40 years, usually with advanced disease stage.

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No rise in the incidence of this cancer has been registered, and it is unclear whether poor prognosis in patients under 40 years correlates with more aggressive tumor type or late diagnosis [3].

The aim of this study was to register and compare localization, clinical and pathological characteristics and survival of sporadic colorectal cancer in patients under 40 and over 65 years of age.

Patients and methods

The medical records of all of the patients with sporadic colon cancer treated at the Institute of Oncology and Radiology of Serbia, Beograd, between January 1998 and December 2002 were retrospectively analyzed. Patients were divided in two groups: group I - 19 patients under 40 years of age (8 males, 11 females) with median age of 32 years (range 25-40 years); and group II-28 patients over 65 years of age (12 males, 16 females) with median age of 69 years (range 65-73 years). All diagnostic and therapeutic decisions were made by the hospital's Joint Committee.

All patients had pathologically confirmed colon adenocarcinoma (during surgery or by endoscopic tumor biopsy).

Pretreatment evaluation included detailed clinical examination, serum biochemistry with liver function tests, full blood count, chest X-ray, abdominal ultrasonography and/or computerized tomography of the abdomen and pelvis. Serum levels of CEA and CA 19.9 were also estimated.

Preoperative staging was done according to the TNM system and postoperatively the patients were classified by the Astler-Coller staging classification. Pretreatment performance status was assessed according to the Karnofsky's index. This study did not include patients with family history of colon cancer or inflammatory colon disease.

Group I TNM stage distribution was as follows: T2N0M0 1 patient, T2N1M0 1 patient, T3N0M0 8 patients, T3N1-2M+ 6 patients, T4N1-2M+ 3 patients.

Group II TNM stage distribution was as follows: T2N0M0 1 patient, T3N0M0 20 patients, T3N1-2M0 2 patients, T3N0M+ 5 patients (Table 1).

Surgical treatment

Right hemicolectomy with ligature of the right and middle colic arteries was performed in cecal and ascending colon cancer. Hepatic flexure tumors were treated with extended right hemicolectomy, including ligation of the main branch of the middle colic artery. Transverse colon cancer was treated with transversectomy with wide omentum resection.

Table 1. Patient and tumor characteristics

	Group I *< 40 years*	*Group II* *> 65 years*	*p-value*
Total patients, n	19	28	
	n (%)	n (%)	
Sex			
males	8 (42)	12 (42)	NS
females	11(58)	16 (58)	
Clinical symptoms			
pain with irregular stools	2	1	
pain with bleeding	3	15	
pain during defecation	0	5	
irregular stools	1	1	
bleeding without pain	2	3	
ileus	1	5	
anemia	0	4	
abdominal pain	5	9	
epigastric pain	1	0	
Metastases at diagnosis			
liver	1	5	NS
lymph nodes	11	2	
ovary, vagina, adnexa, uterus	4	0	
peritoneum with ascites	1	0	
capsule of the right kidney	1	0	
stomach	1	0	
duodenum	1	0	
Tumor localization			
rectum	9 (47.43)	11 (39.6)	NS
left colon	2 (10.5)	6 (21.6)	
transverse colon	3 (15.3)	2 (7.2)	
right colon	5 (26.3)	8 (28.9)	
multiple tumors	0 (-)	1 (3.6)	
T stage			
T1	0 (-)	0 (-)	x^2, p=0.05
T2	2 (10.5)	1 (3.6)	
T3	14 (73.78)	27 (96.4)	
T4	3 (15.3)	0 (-)	
Astler-Coller stage			
A	0 (-)	0 (-)	NS
B	2 (10.5)	3 (10.7)	
C	12(63.24)	20(71.3)	
D	5(26.3)	5 (17.9)	
Tumor grade			
I	1 (5.3)	1 (3.6)	NS
II	11 (57.97)	22 (79.4)	
III	7(36.9)	5(17.9)	
Nuclear grade			
N1	0 (-)	0 (-)	Fisher, p=0.06
N2	19 (100)	22 (79.4)	
N3	0 (-)	6 (21.6)	

NS: non significant

Left hemicolectomy was performed in tumors of the splenic flexure including ligation of the left branch of the middle colic artery.

Descending colon tumors were also resected with left hemicolectomy, including ligation of the same artery. Tumors of the sigmoid colon were resected by the Dixon and Hartman operation, including tying of the main part of the lower mesenteric artery and hemoroidalis superior artery. Rectal cancers were resected using the Milles' procedure.

Chemotherapy

Adjuvant chemotherapy was given to patients with C2 stage, about one month postoperatively as follows: 5-fluorouracil (5FU) 450 mg/m^2/day as 60-min i.v. infusion for 5 consecutive days with folinic acid 20 mg/m^2 i.v. bolus, 45 min before 5FU administration. Courses were repeated every 4 weeks for a total of 6 cycles. The same combination was given to patients with metastatic disease. Toxicity was defined according to WHO toxicity criteria.

Radiotherapy

No adjuvant radiotherapy was used. Palliative radiotherapy was delivered to some patients with metastatic disease.

Follow-up

The patients were evaluated every 3 months in the first year, every 4-6 months in the second year, and every 6 months in the third and fourth year. After 5 years the patients were examined yearly. Tumor markers, abdominal ultrasonography and serum biochemistry were carried out in every examination. Chest radiography was done every 6 months during the first 2 years, and then once a year. Colonoscopy or barium enema were done every 3-4 months during the first year, every 6 months in the second year and yearly thereafter.

Statistics

The following statistical methods were used for analysis of the collected data: arithmetic mean with standard deviation, Fisher's exact test, Student's *t* test, x^2 test and Kaplan-Meier method.

Results

In group I patients the most common symptom was diffuse abdominal pain followed by pain and blood in stool, and also pain with irregular stools and painless bleeding. Anemia and weight loss were not detected in any patient, regardless of abdominal pain. In group II patients the most common symptom was abdominal pain with blood in stool. Diffuse abdominal pain and blood in stool were equally present, as well as ileus and anemia, which was not the case in group I patients (Table 1).

All group I patients had disseminated disease at operation (Table 1). In contrast, only 25% of group II patients had metastases at operation (Table 1). In both groups cancer was dominant in the left part of the colon, while cancer of the right colon was equally present. No significant differences between the 2 groups concerning patient and tumor characteristics were seen (Table 1). Stage distribution is shown in Table 1. No stage A was found in either group and stage B was equally present in both groups (1.5%); stage C was the most frequent stage found in both groups (72.5% and 84.5% in group I and II, respectively); stage D was found in 26% and 14% in group I and II, respectively. All patients had invasive adenocarcinoma. Histological details are shown in Table 1. Tumor grade II and nuclear grade 2 predominated in both patient groups (Table 1).

Hartman's operation was performed in only 10% of group II patients. Other operational procedures were equally used in both groups. No postoperative death occurred.

Postoperative adjuvant chemotherapy was given to 13 (68.4%) group I patients and to 20 (71.4%) group II patients. No adjuvant postoperative radiotherapy was used, while palliative radiation therapy was delivered to 2 (10.5%) group I and 3 (10.7%) group II patients. Two patients from group II received only symptomatic treatment, due to poor general condition. Acute complications from chemotherapy or radiotherapy were not seen.

Local or distant failures were analyzed during a 5-year follow-up. After one year, local relapse and distant metastases were registered in 36% of group I and 42% of group II patients (Table 2). Local recurrences and liver metastases predominated.

Five-year overall survival for both groups was 40.4%, with 57.8% and 28.5% of patients in group I and II, respectively, surviving for 5 years ($p=0.053$; Figure 1). Analysis of 5-year overall survival in relation to tumor localization, time to relapse and mortality showed that the greatest mortality was connected with rectal cancer in both groups (Table 3). Five-year mortality in relation to stage is shown in Table 4. Table 5 depicts 5-year overall survival in relation to stage. Of stage C patients, 75% in group I and 40% in group II survived 5 years. Interestingly, 1 group I stage D patient survives for 5 years.

Table 2. Time to relapse and metastatic localization

	Group I (<40 years)						*Group II (>65 years)*					
Years	*1*	*2*	*3*	*4*	*5*	*total*	*1*	*2*	*3*	*4*	*5*	*total*
	No. of patients						*No. of patients*					
liver	4			1	1	6	5	3				8
lungs					2	2	1		1			2
bones			1			1		1	1			2
local recurrence	2	2	3		1	8	3	2	1			6
ascites	1					1	3	2				5

Table 3. Mortality in relation to primary tumor localization during 5-year follow-up

	Group I (<40 years)						*Group II (>65 years)*					
Years	*1*	*2*	*3*	*4*	*5*		*1*	*2*	*3*	*4*	*5*	
	No. of patients						*No. of patients*					
Rectum (n=9)							*(n=11)*					
liver	1				1			2			2	
liver+ lungs				1	1							
local recurrence		1			1							
local recurrence + vagina			1		1							
ascites+bones+liver			1		1							
liver+local recurrence								2	1		3	
peritoneum									1		2	
lungs+ascites									1		1	
ascites+peritoneum								1	1		2	
						Total 5/9						*Total 10/11*
Left colon (n=2)							*(n=6)*					
liver									2	1	3	
liver+lungs+local recurrence				1	1							
liver+ascites+peritoneum									1		1	
						Total 1/2						*Total 4/6*
Transverse colon (n=3)							*(n=2)*					
liver								1			1	
						Total 0/3						*Total 1/2*
Right colon (n=5)							*(n=8)*					
liver	1				1			2	1		3	
liver+lungs										1	1	
liver+local recurrence+ ascites+peritoneum									1		1	
local recurrence +fistula	1				1							
						Total 2/5						*Total 5/9*

Table 4. Five-year mortality in relation to Astler-Coller stage

	Group I (<40 years)							*Group II (>65 years)*						
Years	*1*	*2*	*3*	*4*	*5*	*total*		*1*	*2*	*3*	*4*	*5*	*total*	
Stage														
B (n=2)		1				1/2*	(n=3)	1	2				3/3	
C (n=12)	1		1		1	3/12 (25%)	(n=20)	2	7	2	1		12/20 (60%)	
D (n=5)	4					4/5 (80%)	(n=5)	5					5/5 (100%)	

p=1.00; *dead/alive

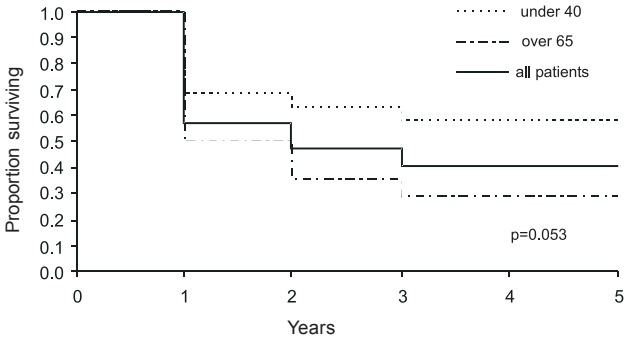

Figure 1. Overall five-year survival.

Discussion

Our results in relation to sex, clinical symptoms and disease stage on presentation were similar to those reported by other authors [4]. The most common symptom in both groups was abdominal pain followed by blood in stool. At diagnosis, 31% of younger population and 24% of older population had distant metastases.

Behbehani et al. [5] studied a group of 56 patients younger than 40 years. Nine of them were lost to follow-up, leaving 47 patients (29 females and 18 males, or 1.6/1.0 ratio) for analysis. This group was compared with a group of 281 out of 525 patients subjected to curative surgery with a median age of 68 years and followed-up for at least 5 years. The female to male ratio was 1.0/1.03. The predominant disease symptom in both groups also was pain with blood in stool and at diagnosis 46.77% (244 out of 525 patients) of the younger and 3.43% (18/525 patients) of the older population had distant metastases. In both patient groups rectal cancer prevailed (47% in the younger and 39% in the older group of patients). These results were confirmed by other authors as well [4-7].

Regarding TNM stage, other authors reported results similar to ours. Mitry et al. [8] reported that T3 stage is highly present in younger population, and T2 in patients of older age. Parramore et al. [9] also reported higher presence of T3 and T4 disease stage in patients up to 40 years in comparison to patients of older age.

Analysis of histological tumor characteristics (histological tumor grade, nuclear tumor grade and presence of mucinous tumor forms) showed that our results were similar to those reported by other authors. Singh et al. [10] reported significantly higher incidence of poorly differentiated tumors of grade III and nuclear grade 3 in 26 patients up to 40 years and 65 patients over 60 years, as well as presence of mucinous tumor forms (p=0.000) in patients up to 40 years compared with older population. Shen et al. [11] found higher incidence of grade III adenocarcinoma with mucinous component also in the group of patients up to 30 years in comparison with older population. De Silva et al. [12] compared 60 patients up to 40 years diagnosed with colorectal cancer, and 245 patients of older age, and found that mucinous and signet-ring cell cancers were significantly more common in the younger age group. However, Behbehani et al. [5] did not find statistical significance comparing the histological tumor type in relation to relapse in 47 colorectal cancer patients aged up to 40 years and 281 patients with a median age of 68 years. Poorly differentiated and mucinous tumors had a locoregional recurrence rate of 21% *versus* 6.6% of moderately well differentiated (p=0.2).

In our study, no patient in either group had stage A. In both groups stage B was identical (1.5%), while 72% of group I and 84.5% of group II patients had stage C. Stage D had 26% and 14% of group I and II patients, respectively.

In a group of 94 patients aged under 40 years Kathryn et al. [13] did not find cases in stage A; 19 patients had stage B, 33 stage C, and 42 stage D. The same authors did not find patients in stage A in older population either.

In their group of 47 patients under 40 years, Behbehani et al. [5] reported only one patient in stage A, 2 patients in stage B, 26 patients in stage C and 18 patients in stage D. No statistical significance regarding stage was found after comparison of this group with another group of 281 patients with a median age of 68 years.

In our study postoperative palliative radiation therapy was delivered to 10% of the patients, and adjuvant chemotherapy was administered to 68% of group I and to 71% of group II patients with good tolerance. Our results (excluding radiotherapy because of insufficient number of patients) are in agreement with those obtained by other authors [14, 15].

In the first year of follow-up 36% of group I and 42% of group II patients developed local or distant failure, mainly in the liver. Behbehani et al. showed similar

Table 5. Five-year overall survival in relation to Astler-Coller stage

Stage	*Group I (<40 years, n=19) Patients, n(%)*	*Group II (>65 years, n=28) Patients, n(%)*	
B	1	0	
C	9 (75)	8 (40)	
D	1	0	
Total	11 (57.8)	8 (28.5)	p=0.053

Both groups, overall survival 19/47=40.43%

results in their study where, after primary treatment, disease relapse developed in 76% of patients under 40 and in 65% of patients of older age; liver metastases were verified in 35% of the patients in both groups [5].

Analysis of 5-year survival of our patients showed that our results differed from those of other investigators. Due to the absence of stage A patients and the small number of stage B patients in both groups of our study, no reliable comparisons could be done with similar studies of other authors.

In our study stage C 5-year overall survival in group I and II was 75% and 40%, respectively. Five-year overall survival in group I and II was 57.8% and 28.5%, respectively, and 5-year overall survival in both groups was 40.4%. Paraf et al. [16] found no significant difference in 5-year survival in relation to stage in their 34 patients under 40 years and 34 patients over 65 years. Similarly to previous authors, Paramore et al. [9] did not find statistical significance in 5-year survival in patients under 40 and over 55 years. In an analysis by Minardi et al. [17] in their group of 37 patients with colorectal cancer under 40 years, stage C was present in 37% and stage D in 22% of the patients. Five-year survival in stage C was 11% and zero in stage D. Five-year overall survival was 26% (5 patients aged 19 years), and it was much worse in patients of older age [17]. Farrington et al. also reported worse 5-year survival in their group of patients under 40 years, compared with patients of older age [18]. Singh et al. reported that 2-year overall survival was significantly lower in younger patients in comparison to older ones (4% *versus* 55%, p= 0.003) [10].

Similarly to the previous authors [6,16] Gunel et al. concluded that 5-year survival was also worse in younger population, compared with older patients [19].

However, results of Turkiewicz et al. [20] showed better 5-year survival in younger patients compared to older ones. Similarly to our results, these authors reported 5-year survival in 53% of younger patients.

Our results of 5-year overall survival are also in agreement with those reported by Mitry et al. who found better 5-year overall survival in the group of patients under 40 years [8].

We conclude that aggressive tumor forms are more often present in younger population but do not contribute to poorer 5-year survival.

Longer survival is possible with early diagnosis, radical surgical treatment, and aggressive chemotherapy or chemoradiotherapy.

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