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Trends in pathology in colorectal cancer patients in Serbia 2003-2016

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Abstract

Colorectal cancer (CRC) is a leading cause of morbidity and mortality worldwide, with varying trends in tumor pathology depending on geographic and demographic factors. The aim of this study was to describe trends in tumor pathology in Serbian patients with colorectal cancer (CRC) over a 14-year period, from 2003 to 2016. The study included patients referred from local units to the tertiary center for CRC treatment during the entire observation period, as well as patients diagnosed within the national screening program during the last four years. Resections were performed in 2462 patients (1465 men, 60% and 997 women, 40%) with an average age of 62±12 years, and the incidence was equally distributed between genders. Rectal tumors were noted in 54% of patients, while in 46% of patients tumors were found in the colon (32% in the left and 14% in the right colon). The majority of patients were in an advanced stage of the disease, with only 12% of cases with Dukes A stadium. Patients with early-onset disease represented between 11% and 22% of all cases per year. Among early-onset patients, women were significantly overrepresented (P=0.013), patients were diagnosed at significantly later stages (P=0.033), tumors were significantly less differentiated (P=0.001) and tumors of the right colon were overrepresented (P<0.001). A group of patients who underwent neoadjuvant chemoradiotherapy consisted of 235 men and 88 women with an average age of 60±12 years. Within this group, 20% of patients had a good response, 37% a moderate response, and 43% a poor response. The study has provided valuable insight into trends in tumor pathology in Serbian CRC patients and confirmed the beneficial effects of the introduction of the national screening program.

Introduction

In spite of the therapeutic advancements, CRC remains a heavy burden for the world health systems. It is the third most deadly and fourth most commonly diagnosed cancer in the world (1). The incidence of this disease has increased substantially during the last four decades mainly due to primary preventable factors, and the incidence is expected to continue increasing during the next decades mainly due to further aging of the population (2). There is a specifically alarming rise in incidence of early-onset CRC, which differs in epidemiological, clinical, pathological, and molecular features from late-onset disease (3). The incidence and mortality of this disease among the individuals younger than 50 has risen by about 2% and 1.3% annually, respectively (4). Although these rates are considerably lower than in older adults, a disturbing pattern is beginning to emerge considering aggressive features and worse outcomes in early-onset disease.

During the last two decades, management of colorectal cancer (CRC) has significantly advanced. Improved surgical approaches and introduction of a watch-and-wait strategy after neoadjuvant chemoradiotherapy (nCRT) resulted in better outcomes for patients (5). Incorporation of molecular data in the clinical management of patients will allow

further advancement towards precision medicine. New classifications of CRC are emerging, based on molecular parameters: combinations of gene expression patterns, chromosomal alterations, gene mutations and epigenetic determinants (6). Since these analyses are rather expensive, they are still mostly used for research and development of novel therapies. Therefore, the input of the pathologist remains crucial for diagnosis, risk stratification and choice of treatment in routine clinical practice (7).
The aim of this study was to describe trends in tumor pathology in Serbian patients with colorectal cancer in the period 2003-2016. Additionally, the study aimed to provide insight into the pathological features of early-onset CRC and response to standard nCRT.

Material and methods
The study was conducted in a tertiary care unit. Data on all patients who underwent operative CRC resection between 2003 and 2016 were included in the electronic database. Collected data included demographic data, surgical information and pathology findings. The following data on the tumor pathology were included in the analysis: tumor position, tumor dimensions, type of macroscopic tumor growth, histopathological type of tumor according to the 2019 WHO release (8), stage of TNM tumor disease according to the 9th edition of American Joint Committee on Cancer (9), the degree of tumor differentiation, and the classification of residual status. Stages of tumor disease were analyzed using systems according to the Dukes and Aster Coller classification.
The tumor pathological features of the subgroup of patients under 50 years of age were compared with the rest of the cohort.
Pathological response to the standard nCRT regimen (45 Gy delivered in 25 daily fractions over 5 weeks with concurrent 425 mg/m of 5-fluorouracil and 20 mg/m2 of leucovorin) was assessed based on histological examination of the resected specimens according to the Mandard tumor regression grade (TRG) classification system (10).
Statistical analysis was performed by the Statistical Package for Social Sciences 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequencies. The differences between categorical variables were analyzed by Fisher's exact test and Pearson $\chi 2$ test. A p value less than 0.05 was considered statistically significant.

Results
The observed 14-year period (2003-2016) encompassed 2462 surgical resections of CRC. The annual number of resections varied between 88 and 286, with an average of 175 per year. The resections were conducted in 1465 men (60%) and 997 women (40%) with an average age at diagnosis of 62±12 years (Figure 1).

Characteristics of patients with early-onset and late-onset disease are given in Table 1. Differences in demographic and pathologic characteristics were tested between young adults and older individuals. Among early-onset patients, women were significantly overrepresented (P=0.013), patients were diagnosed at significantly later stages (P=0.033), tumors were significantly less differentiated (P=0.001) and tumors of the right colon were overrepresented (P<0.001). Patients with early-onset disease represented between 11% and 22% of all cases per year, with an average of 15.6% (Figure 2). In 2014 and 2016, a significant reduction in the number of CRC cases was observed among patients aged over 50. Specifically, the incidence of CRC in this age group showed a noticeable decline during these years compared to previous years (Figure 2). This reduction may reflect broader trends in CRC detection and management, particularly

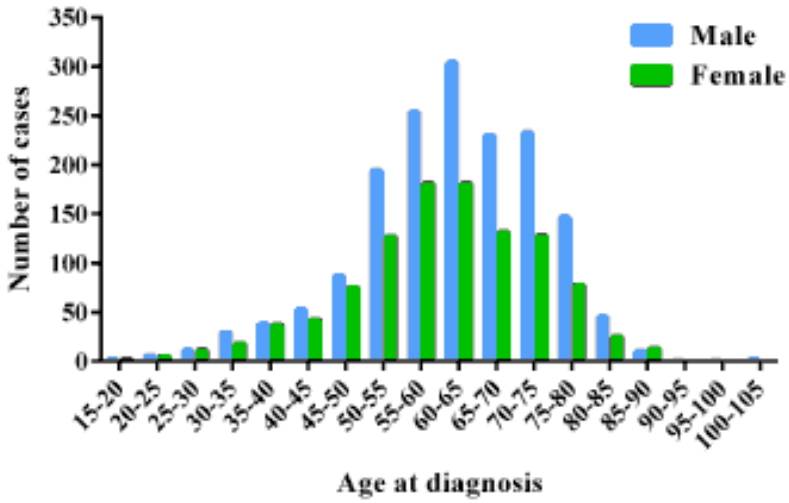

Figure 1. Frequency of surgical CRC resection cases according to sex and age

related to the introduction of the national screening program in 2013.
In 54.1% of cases, the tumors were localized in the rectum (Figure 3). Of the colon tumors, 31.9% were localized in the left colon and 14% in the right colon.
A group of patients with LARC who underwent nCRT consisted of 235 men and 88 women with an average age of 60±12 years. Within this group, 20% of patients had a good response (TRG1+TRG2), 37% a moderate response (TRG3), and 43% a poor response (TRG4+TRG5) (Table 2).

Table 1. Characteristics of the analyzed group of CRC patients

	All patients (N=2462)	=50 years (n=385)	>50 years (n=2077)
Male gender (%)	60	54	61
Average age ± SD (years)	61.7±12.3	41.1±7.9	65.5±8.7
Localization (%)			
Rectum	54	45	55
Left colon	32	31	32
Right colon	14	24	13
Differentiation grade (%)			
G1	63	57	65
G2	29	30	28
G3	8	13	7
Dukes (%)			
A	12	14	12
B	37	29	38
C	47	51	46
D	4	6	4
Astlercoller (%)			
A	3	3	3
B1	14	14	13
B2	32	25	33
B3	2	3	2
C1	3	1	3
C2	35	41	34
C3	7	7	8
D	4	6	4

Discussion
This study aimed to provide insight into the epidemiology of surgical cases of colorectal cancer in Serbia, with a focus on trends in pathology among individuals with early onset disease and patients subjected to nCRT. For this purpose, a large amount of data was collected, covering 14 years of practice in a tertiary care unit.
Our study looked at the pathological and demographic characteristics associated with colorectal cancer at diagnosis. The study showed that the majority of patients who underwent CRC resection in the observed period were males (60%). This fits with data collected from all age groups and nations, which show that males are approximately 1.5 times more likely to develop CRC than females (11). Some studies suggest that this might be due to a shorter life expectancy

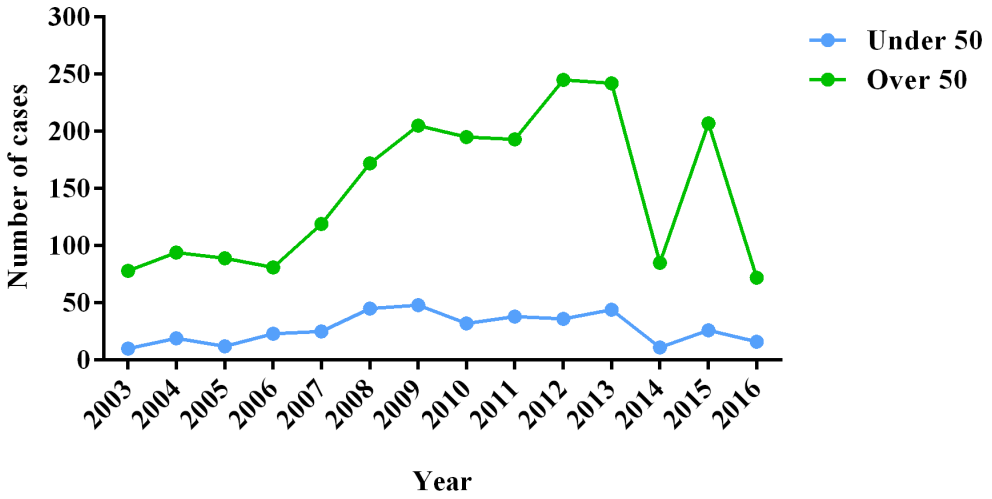

Figure 2. The number of early-onset and late-onset CRC cases

of males or the role of the sex steroid hormone estrogen in CRC development (12, 13). The data of the countries in the region also indicate a larger number of males affected by CRC than females (14, 15). Women with early-onset disease are slightly more frequent than overall, which was confirmed by our study (46% vs. 40%).

The majority of patients were in the sixth or seventh decade (average age of 62±12 years), with 15.6% of all cases being early-onset patients (≤50 years). This finding is expected considering that old age is an acknowledged risk factor for CRC and that the risk of developing the disease increases with age (16, 17). Distribution across age categories was similar in males and females. The peak incidence occurred in the age group of 60–65. The incidence of CRC is increased after the age of 50 years and the average age at the time of the diagnosis is around 64 years (18, 19). The incidence of CRC is higher in highly developed countries, which is explained by the fact that the modernization of society and increased living standards also affect the development of health care (18). As a result, the life expectancy of citizens is increased, and thus the frequency of CRC cases in the population (20). The rise in the number of cases in Eastern Europe appears to be due to westernization and an unhealthy lifestyles that includes poor diet and reduced physical activity (14). In the analyzed 14-year period, the number of late-onset CRC cases increased over the years and there was also a slight increase in the incidence of early onset cases, reflecting the global trend observed during the past couple of decades (21). This is in line with the increasing number of all CRC cases globally, and may be partly due to the improved detection of the disease. Several studies point to the increase in incidence of early-onset cases (12, 18, 22). On the other hand, the frequency of early-onset disease slightly declined during the final years of the observation period, and the average value of 15% is lower than in the majority of other similar studies where early-onset patients represented 20% or more of the analyzed group (23, 24). In general, younger patients appear to have more distal or rectal disease, a more advanced stage of disease at presentation, and more unfavorable histological features, and the results of our study align with these findings (24-26).

Until 2014, the patients were more frequently diagnosed at the advanced stage of CRC. Since then, the slight decrease has been observed, which can be explained by the introduction of the national screening program. Serbia joined the majority of European countries conducting national CRC screening programs in 2013 by extending the local programs that had been active in three municipalities since 2005 (27, 28). The program is based on the immunochemical faecal occult blood test (iFOBT) and it is offered to 50-74 year olds without evidence of CRC. The rate of participation is around 60%.

The disease was observed to affect the rectum more frequently than colon, with the incidence of the right colon disease of 14%, which was overrepresented in younger patients. The colon being affected in less than half of the cases is a different pattern than in most developed countries, where the declining frequency of rectal cancer was observed (2, 29). The disproportionately high proportion of rectal cancers in this cohort (54%) compared to the expected ~35% in general CRC populations could be explained by referral bias, since this study was conducted at a tertiary care center, patients with rectal cancers, which often require more complex management and have different treatment protocols (e.g., neoadjuvant chemoradiotherapy), may have been more likely to be referred to this specialized facility, and colon cancer surgeries can be performed in secondary centers, while rectal cancer surgeries are usually centralized at tertiary institutions. This could lead to a higher representation of rectal cancer cases in our cohort.

Fluctuations in the ratio between right-sided and left-sided lesions in different populations may be due to the diagnostic improvements, namely the application of the complete colonoscopy instead of the earlier most commonly applied rigid rectoscopy (29). The frequency of the right colon lesions was significantly lower in our study in comparison to the results that came out of the national screening program in 2016, when 29.6% of polyps and 22.7% of the carcinomas

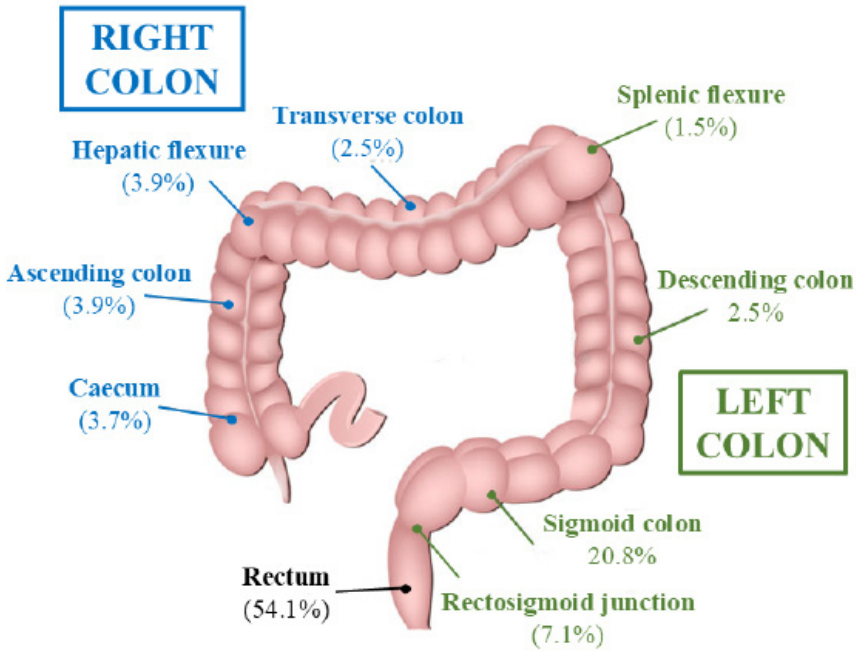

Figure 3. Distribution of tumors according to the localization

Table 2. Frequency of LARC cases subjected to nCRT according to the response

Response category	TRG	% of patients	average age	% of men
complete	1	3	57.2	70.0
good	2	17	56.5	67.3
moderate	3	37	60.8	75.0
poor	4	37	59.9	72.5
none	5	6	58.4	70.0

were found in the proximal parts of the colon of subjects with the positive diagnosis on colonoscopy (30). The results of the national screening program correspond to the findings from other countries (31). This discrepancy could be due to the fact that subjects in the national screening program are recruited directly from the general population, while surgical cases included in our study are those referred to the tertiary care center from the local healthcare institutions. In the subgroup of patients who underwent nCRT, there was an unexpectedly low rate of complete pathological response (3%) when compared to the data collected from other populations (over 10%) (32). These patients are candidates for the watch-and-wait approach, an evolving alternative to radical surgery aiming for organ preservation and improved quality of life (5). The other group of interest is patients with no response (TRG5), as they are candidates for other therapeutic modalities since nCRT appears to be non-beneficial for them. In our study, 6% of patients were classified as non-responders. Overall, patients with good response were slightly younger, and there were slightly more women among them.

This study has several limitations that should be acknowledged. As a retrospective, single-center analysis, it may not fully represent the broader CRC population in Serbia or other regions, thereby limiting the generalizability of the findings. Patients referred to a tertiary care center are more likely to have advanced or complex disease, which may skew the distribution of tumor stages and treatment outcomes. Another limitation of our study was the unavailability of follow-up data, which was due to the fact that most patients who underwent surgery at the clinic where the study was conducted do not return for control examinations. The absence of structured follow-up data prevents evaluation of long-term outcomes such as recurrence or survival, which are essential for assessing the prognostic significance of pathological findings and treatment responses. The study also lacked molecular profiling, which is increasingly relevant in CRC classification and personalized treatment planning. These limitations highlight the need for prospective, multicenter studies incorporating comprehensive clinical, pathological, and molecular data, as well as robust follow-up

protocols, to better inform CRC management and outcomes in diverse populations.

Conclusion
Our study provides valuable insight into trends in tumor pathology in Serbian CRC patients and confirms the beneficial effects of the introduction of the national screening program.

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Declaration of conflicting interest - The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement
The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024. All patients signed an informed consent.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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