Original Article
Comparison of survival and pathological features of signet-ring cell carcinoma of the colon between young and elderly patients

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Abstract: Background: Signet-ring cell carcinoma (SRCC), a rare histological type of colon cancer, is associated with aggressive biological behavior and poor prognosis. Here, we aim to compare the clinicopathological features and the survival outcomes between young and elderly patients with SRCC of the colon without distant metastasis. Methods: We analyzed patients with non-metastatic SRCC of the colon in the Surveillance, Epidemiology and End Results (SEER) database. Patients were divided into three groups based on age: group 1 (≤30 years), group 2 (30-60 years) and group 3 (>60 years). A multivariate Cox proportional hazards model was performed to analyze risk factors for cancer-specific survival (CSS). Results: In all, 803 patients were included in the analysis. A higher proportion of stage III disease and N2 disease was found in patients in group 1 compared with patients in group 2 and group 3. The Kaplan-Meier analysis showed increasing CSS with increasing age (P<0.001): the 5-year CSS was 21.9% for patients in group 1, 52.3% for patients in group 2 and 56.6% for patients in group 3. A multivariate analysis indicated that age was an independent prognostic factor for CSS (P=0.045). Compared with patients in group 1, patients in group 2 were more likely to exhibit a greater CSS (HR 0.610, 95% CI 0.413-0.900, P=0.013), as were patients in group 3 (HR 0.673, 95% CI 0.454-0.997, P=0.048). Conclusions: Young patients are associated with poor CSS, as well as with advanced tumor stage and extensive lymph node involvement in SRCC of the colon without distant metastasis.

Keywords: Colon cancer, signet-ring cell carcinoma, age, survival

Introduction

Colon cancer is one of the major causes of cancer-related morbidity and mortality worldwide, with over 90,000 new cases and 40,000 deaths estimated to occur in the United States in 2016 [1]. A progressive decline in the incidence of colon cancer has occurred over the past three decades [1], but the rates of signet-ring cell carcinoma (SRCC), a rare but distinct form of colon cancer, have slightly increased [2].

SRCC, which is characterized by prominent intracytoplasmic mucin in more than half of all tumor cells [3], constitutes approximately 1% of all colorectal cancer cases [4-7]. Colorectal SRCC is correlated with poor pathological features, such as poorly differentiated lesions [4, 5], perineural or lymphovascular invasion [4, 8], and lymph node metastasis [7, 9]. As for the prognosis, SRCC is suggested to be an independent risk factor for unfavorable outcomes in colorectal cancer by the American Joint Committee on Cancer (AJCC) cancer staging manual (7th edition) [10]. A large population-based study, including approximately two hundred thousand colorectal cancer patients, showed that 7.7% of SRCC patients, but only 2.7% of adenocarcinoma patients, were under the age of 45 years [6]. Although young-onset colon cancer has long been notorious in cases of SRCC [11, 12], poor differentiation [12, 13], and late-stage presentation [11-13], numerous studies have reported comparative [14-16] or even significantly better [11, 12] survival outcomes in young patients compared with their older counterparts.

Notably, current knowledge on this issue is primarily derived from series that assessed the prognostic value of age in various ethnic popu-

Table 1. Demographics of patients with non-metastatic signet-ring cell carcinoma of the colon from the SEER database, stratified by age at diagnosis [N (%)]

Characteristics	Total	Group 1 (≤30 y)	Group 2 (30-60 y)	Group 3 (>60 y)	Group 1 vs 2	Group 1 vs 3	Group 2 vs 3
			Age groups			P value	
	(N=803)	(N=49)	(N=362)	(N=392)			
Median follow-up (months)	27	20	30	26			
Sex					0.585	0.973	0.286
Male	442 (55.0)	26 (53.1)	207 (57.2)	209 (53.3)			
Female	361 (45.0)	23 (46.9)	155 (42.8)	183 (46.7)			
Year of diagnosis					0.610	0.154	0.064
1988-2003	322 (40.1)	23 (46.9)	156 (43.1)	143 (36.5)			
2004-2011	481 (59.9)	26 (53.1)	206 (56.9)	249 (63.5)			
Primary site					0.154	<0.001	<0.001
Right colon	638 (79.5)	32 (65.3)	271 (74.9)	335 (85.5)			
Left colon	165 (20.5)	17 (34.7)	91 (25.1)	57 (14.5)			
Race					0.244	0.008	0.050
White	662 (82.4)	34 (69.4)	289 (79.8)	339 (86.5)			
Black	86 (10.7)	9 (18.4)	45 (12.4)	32 (8.2)			
Other *	55 (6.9)	6 (12.2)	28 (7.8)	21 (5.3)			
Pathological grade					0.815	0.955	0.540
Well/Moderate	85 (10.6)	5 (10.2)	41 (11.3)	39 (9.9)			
Poor/Undifferentiated	718 (89.4)	44 (89.8)	321 (88.7)	353 (90.1)			
Tumor size					0.791	0.761	0.939
≤5.0 cm	377 (46.9)	24 (49.0)	170 (47.0)	183 (46.7)			
>5.0 cm	426 (53.1)	25 (51.0)	192 (53.0)	209 (53.3)			
T stage					0.617	0.235	0.168
T1	30 (3.7)	2 (4.1)	15 (4.2)	13 (3.3)			
T2	31 (3.9)	0 (0)	12 (3.3)	19 (4.8)			
T3	469 (58.4)	27 (55.1)	201 (55.5)	241 (61.5)			
T4	273 (34.0)	20 (40.8)	134 (37.0)	119 (30.4)			
N stage					0.002	<0.001	0.071
N0	209 (26.0)	2 (4.1)	87 (24.0)	120 (30.6)			
N1	184(22.9)	9 (18.4)	82 (22.7)	93 (23.7)			
N2	410 (51.1)	38 (77.5)	193 (53.3)	179 (45.7)			
TNM stage					0.006	<0.001	0.121
Stage I	39 (4.9)	1 (2.0)	17 (4.7)	21 (5.3)			
Stage II	170 (21.1)	1 (2.0)	70 (19.3)	99 (25.3)			
Stage III	594 (74.0)	47 (96.0)	275 (76.0)	272 (69.4)			

*Includes Native American, Asian, Pacific Islander and Unknown.

lations or in patients with different stages of colorectal cancer. However, very little data are currently available on the role of age in a particular histological subtype. We hypothesized that young patients with non-metastatic SRCC of the colon may be a biologically aggressive phenotype and may have a poorer prognosis than elderly patients. To address this hypothesis and to compare the clinicopathological features betw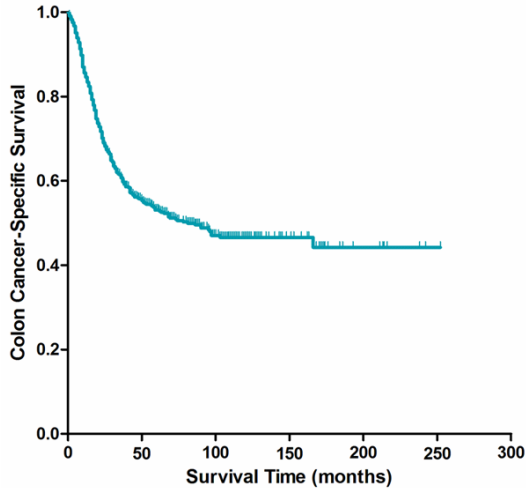een young-onset SRCC of the colon and their older counterparts, we analyzed a subset of patients in the Surveillance, Epidemiology, and End Results (SEER) database with non-metastatic SRCC of the colon.
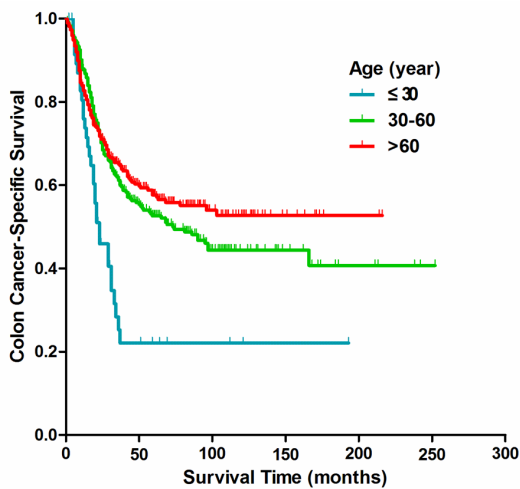
Materials and methods

Patient selection

The Surveillance, Epidemiology and End Results (SEER) database, which contains information

Figure 1. Kaplan-Meier curves for patients with non-metastatic signet-ring cell carcinoma of the colon from the SEER database.

Figure 2. Kaplan-Meier curves for patients from the SEER database with signet-ring cell carcinoma of the colon without distant metastasis, stratified by age at diagnosis.

on 18 cancer registries that cover 26% of the U.S. population, collects and provides cancer incidence and survival data. Cases of invasive colon cancer from January 1988 to December 2011 were extracted from the database (http://seer.cancer.gov, April 2013 release). We included patients from the SEER database who met the following criteria: (1) age at diagnosis between 18 and 75 years old; (2) SRCC of the colon; (3) known intestinal wall invasion and lymph node status; (4) no fewer than 12 lymph nodes harvested; (5) colon cancer surgically

resected and a pathology specimen obtained; (6) pathologically confirmed SRCC of the colon as opposed to a diagnosis through death certificate or autopsy; (7) non-metastatic (AJCC stage M0); (8) known survival time and cause of death; and (9) colon cancer as the only malignant tumor. Patients were excluded if they underwent only local tumor excision or if they received neoadjuvant chemoradiotherapy (nCRT). The Fudan University Shanghai Cancer Center Ethical Committee and Institutional Review Board reviewed and approved the research protocol.

Outcome measures

Data on the following variables were derived from the SEER database: sex, race, age at diagnosis, pathological grading, year of diagnosis, number of primary tumors, number of lymph nodes examined, number of metastatic lymph nodes (N0, N1 and N2), depth of intestinal wall invasion (T1, T2, T3 and T4), AJCC cancer stage, radiation sequence with surgery, follow-up duration and SEER cause-specific death classification. All cases were restaged based on the 7th AJCC cancer staging system. The cecum, ascending colon, hepatic flexure of the colon, and transverse colon were defined as the right colon, whereas the splenic flexure of the colon, descending colon and sigmoid colon were defined as the left colon. The cancer-specific survival (CSS), which was the primary end point of our study, was calculated from the date of diagnosis to the date of colon cancer-specific death. Deaths from other causes or being alive at the last follow-up were treated as censored observations.

Statistical analysis

Patients from the SEER database with non-metastatic SRCC of the colon were divided into three groups based on age at diagnosis: group 1 (≤30 years of age), group 2 (30-60 years of age) and group 3 (>60 years of age). The clinico-pathological data based on these age groups was summarized using cross-tabulation, and the distributions were compared using chi-squared tests. Survival curves were created using the Kaplan-Meier analysis, and the log-rank test was used to identify differences. A multivariate Cox proportional hazards model was performed to analyze risk factors for survival outcome. All statistical analyses were con-

Table 2. Univariate survival analyses of patients with non-metastatic signet-ring cell carcinoma of the colon from the SEER database

Variable	No.	5-year CSS (%)	Log Rank x^2	P value
Sex			0.798	0.372
Male	442	51.0		
Female	361	53.7		
Year of diagnosis			1.524	0.217
1988-2003	322	50.8		
2004-2011	481	53.1		
Primary site			3.996	0.046
Right colon	638	55.0		
Left colon	165	42.6		
Race			3.949	0.139
White	662	53.8		
Black	86	42.4		
Others*	55	46.2		
Pathology grade			4.657	0.199
Well/Moderate	85	60.2		
Poor/Undifferentiated	718	49.7		
Tumor size			0.051	0.821
≤5.0 cm	377	51.5		
>5.0 cm	426	54.2		
T stage			68.658	<0.001
T1	30	87.9		
T2	31	84.0		
T3	469	59.8		
T4	273	29.2		
N stage			158.488	<0.001
N0	209	88.8		
N1	184	59.5		
N2	410	29.8		
Age at diagnosis (yr)			17.272	<0.001
≤30	49	21.9		
30-60	362	52.3		
>60	392	56.6		

CSS = cancer-specific survival. *Includes Native American, Asian, Pacific Islander and Unknown.

ducted using the SPSS statistical package. All computed *p* values were two-sided, and P<0.05 was considered statistically significant.

Results

Clinicopathological differences among age groups

We included 803 patients from the SEER database with SRCC of the colon. In all, 327 (40.7%) colon cancer-specific deaths were identified. The median follow-up time was 27 months (interquartile range, 11-63 months). These 803 patients were classified into 3 age groups for analysis. Group 1 (≤30 years of age) consisted of 49 patients (6.1%), group 2 (30-60 years of age) consisted of 362 patients (45.1%), and group 3 (>60 years of age) consisted of 392 patients (48.8%). Patient demographics and pathologic characteristics based on the age groups are summarized in **Table 1**.

In regard to tumor location, more tumors were located in the left colon in group 1 (34.7%, P<0.001) and group 2 (25.1%, P<0.001) compared with group 3 (14.5%), but no significant difference was found between groups 1 and 2 (P=0.154). More Caucasians were in group 3 (86.5%) than in group 1 (69.4%, P=0.008), but no significant difference was observed between groups 1 (P=0.244) and 3 (P=0.050) and group 2 (79.8%). Group 1 (77.5%) had a significantly higher proportion of N2 lesions than group 2 (53.3%, P=0.002) and group 3 (45.7%, P<0.001), but no significant difference was found between group 2 and group 3 (P=0.071). As regards to TNM stage, group 1 (96.0%) had a significantly greater percentage of stage III disease than group 2 (76.0%, P=0.006) and group 3 (69.4%, P<0.001); however, the differences between group 2 and group 3 were not significant (P=0.121). Finally, no significant difference (all, P>0.05) among the different age groups was observed with respect to sex, year of diagnosis, pathology grade, tumor size or T stage.

Survival differences among age groups

The Kaplan-Meier curves for patients from the SEER database with non-metastatic SRCC of the colon are illustrated in **Figure 1**, which shows that the one-year CSS stood at 83.9%, the three-year CSS at 59.8%, and the five-year CSS at 52.5% for the entire cohort. The Kaplan-Meier analysis showed increasing CSS with

Table 3. Multivariate survival analyses of patients with non-metastatic signet-ring cell carcinoma of the colon from the SEER database

Variables	Multivariate analysis		
	HR	95% CI	P value
Primary site			0.763
Right colon	1	reference	
Left colon	0.961	0.743-1.243	
T stage			<0.001
T1	1	reference	
T2	0.957	0.238-3.848	0.951
T3	1.677	0.615-4.578	0.313
T4	2.784	1.013-7.656	0.047
N stage			<0.001
N0	1	reference	
N1	3.261	2.017-5.272	<0.001
N2	6.877	4.403-10.740	<0.001
Age at diagnosis (yr)			0.045
≤30	1	reference	
30-60	0.610	0.413-0.900	0.013
>60	0.673	0.454-0.997	0.048

HR = hazard ratio, CI = confidence interval.

increasing age (P<0.001): the 5-year CSS was 21.9% in patients ≤30 years of age, 52.3% in patients at 30-60 years of age and 56.6% in patients >60 years of age (**Figure 2**). A univariate analysis of the entire sample indicated that the primary tumor site (P=0.046), T stage (P<0.001), N stage (P<0.001) and age at diagnosis (P<0.001) were risk factors for CSS (**Table 2**). An analysis using the multivariate Cox proportional model identified T stage (P<0.001), N stage (P<0.001) and age at diagnosis (P=0.045) as independent prognostic factors (**Table 3**). Compared with T1 stage patients, T4 stage patients were approximately 3 times more likely to succumb to SRCC (HR 2.784, 95% CI 1.013-7.656, P=0.047). N2 stage patients were more than 6 times more likely to die of SRCC than N0 stage patients (HR 6.877, 95% CI 4.403-10.740, P<0.001). Compared with patients ≤30 years of age, patients at 30-60 years of age were more likely to exhibit a greater CSS (HR 0.610, 95% CI 0.413-0.900, P=0.013), as were patients >60 years of age (HR 0.673, 95% CI 0.454-0.997, P=0.048).

Discussion

Colon cancer is generally considered a disease of the elderly, but younger individuals with this disease have attracted great attention recently due to the upward trend of young-onset colon cancer in many reports over the past several decades [17]. As an example, in the United States, it was reported that the incidence rates of young-onset colon cancer have increased gradually from 1975 to 2006, which is in sharp contrast to the steady decline of the overall incidence and death rates [18]. Although various studies have focused on the clinicopathological characteristics and the prognosis of young-onset colon cancer, the conclusions were not in agreement. Some researchers have suggested a comparable prognosis [14-16], whereas others have reported a better prognosis in young patients [11, 12] compared with older patients.

Colorectal SRCC is considered to be an aggressive histological subtype due to the lack of cell-to-cell adhesions, which may lead to more metastases [9, 19, 20]. Furthermore, colorectal SRCC was also reported along with more cases of locally advanced tumors [7, 21], metastases at multiple sites, especially peritoneal carcinomatosis [9, 19-21], and tumors of advanced TNM stage [5-7]. It is also noteworthy that more young-onset cases have been observed in SRCC of the colon, as opposed to other subtypes of colon cancer [6]. In one study, Benmoussa et al. [22] reported that SRCC and mucinous adenocarcinomas accounted for 18.5% of all colorectal cancer cases in the group of younger patients, whereas these subtypes accounted for 5.1% in the group of older patients, which was in line with the results of other studies [23, 24]. Li et al. [11] evaluated 69,835 patients with colorectal cancer in the SEER Database and found that patients younger than 40 years of age were more likely to be diagnosed with SRCC than those older than 40 years of age (2.8% vs. 0.8%).

The results from our study indicated that in SRCC of the colon without distant metastasis, young patients exhibited a poorer CSS than older patients. In our study, as previously illustrated, a higher proportion of stage III disease and N2 disease was found in younger patients compared with older patients. The advanced

tumor stage and extensive lymph node involvement in cases of young-onset SRCC of the colon may be explained by the fact that most patients mistakenly believe that malignant tumors are unlikely to occur at a young age, and as a result, they typically ignore the clinical symptoms of malignancy. Likewise, in young patients, doctors are less likely to associate these complaints with signs of malignancy, and they may therefore miss the optimal opportunity for treatment. Also, the late occurrence of clinical manifestations in patients with colorectal SRCC [25] and the similarities in radiological appearance with barium enema between colorectal SRCC and Crohn's disease [26] may result in a delay in diagnosis.

In addition, the specific genetic basis of young-onset SRCC of the colon may have contributed to our findings. As the field of molecular biology continues to progress at a rapid rate, various cancer-related genes such as p53, KRAS and APC have been reported to play an important role in the carcinogenesis of colorectal cancer [27]. Colorectal SRCC has also been reported to have a unique genetic basis, including more frequent MSI-H [28] and MLH1 mutations [29], which may contribute to the aggressive behavior and poor prognosis of SRCC. Likewise, young-onset colorectal cancer is also believed to involve distinct genetic events. Greater rates of MSI positivity and a lower frequency of BRAF and KRAS mutations have been observed in young patients with colorectal cancer compared with older patients [30, 31].

However, the definite genetic characteristics of young-onset colorectal SRCC have not yet been revealed. Brooks-Wilson et al. observed a CDH-1 missense mutation in a 35-year-old woman with SRCC of the colon [32]. Moreover, several studies on the genetic basis of SRCC of the stomach may help shed new light on this issue. S. Sugimoto et al. [33] reported the detection of a large genomic deletion of CDH-1 in a 41-year-old patient diagnosed with SRCC of the stomach. Additionally, Guilford et al. [34] and Gayther et al. [35] found that individuals with CDH-1 germ-line mutations may be predisposed to young-onset hereditary diffuse gastric cancer (HDGC), the advanced stage of HDGC was comprised primarily or exclusively of signet-ring cells [36]. It is advised in the guidelines established by the 8th workshop of the International Gastric Cancer Linkage Consortium (IGCLC) to consider early colonoscopy screening in individuals with a CDH-1 mutation who have a family history of colon cancer [36]. Based on these prior studies, we assume that a possible explanation for the poorer prognosis of young-onset SRCC of the colon may lie in the fields of genetics and molecular biology, thus, further studies are expected to explore the genetic features of young-onset colorectal SRCC.

Best to our knowledge, this is the first study to date that specifically compares the clinicopathological features and survival outcomes between patients with young-onset SRCC of the colon and their older counterparts. Because SRCC is a rare histological type, our current knowledge of SRCC is primarily obtained from studies of small population. Therefore, we analyzed patient data from the SEER database to ensure a large sample size and a good reliability. However, the current study still has several limitations. First, because data on family history and molecular biology are not available in the SEER database, we were unable to clarify any genetic or hereditary feature of young-onset SRCC of the colon. Second, one remarkable limitation of the SEER database is that it does not contain records on adjuvant chemotherapy, which limits our ability to analyze the influence of adjuvant chemotherapy on the current findings.

In conclusion, our results provide initial evidence that young patients are associated with poor CSS, as well as with advanced tumor stage and extensive lymph node metastasis in SRCC of the colon without distant metastasis. Further studies are needed to reveal the exact molecular and genetic features of young patients with SRCC of the colon.

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Disclosure of conflict of interest

None.

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