JBUON 2017; 22(1): 170-177
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

The association between small tumor size and poor survival in T4 mucinous adenocarcinoma of colon without distant metastasis

Ben Huang*, Chen Chen*, Mengdong Ni, Xiaomin Xue, Guoxiang Cai, Sanjun Cai

Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China

*These authors contributed equally to this work

Summary

Purpose: *The purpose of this study was to analyze the impact of tumor size on cancer-specific survival (CSS) in patients with mucinous adenocarcinoma (MAC) of the colon, showing heavy intestinal wall invasion without distant metastasis (T4 N0-2 M0).*

Methods: *Patients with T4N0-2M0 MAC of colon were analyzed based on data from the US Surveillance, Epidemiology, and End Results (SEER) database. Survival was analyzed using the Kaplan-Meier method, and the log-rank test was used to identify differences. Risk factors were analyzed using the Cox proportional hazard model. A preliminary analysis of T4N0-2M0 adenocarcinoma of colon patients from the SEER database is also presented.*

Results: *A total of 585 patients from the SEER database were included in the analysis. The cutoff value (5.0 cm) was determined using the X-tile program. Kaplan-Meier analysis showed that tumors ≤5.0 cm had a poorer CSS compared to tumors >5.0 cm (p=0.034). Multivariate analysis indicated that tumor size is an independent prognostic factor for these patients, and compared to tumors ≤5.0 cm, tumors >5.0 cm were more likely to have better CSS (HR 0.658, 95% CI 0.506-0.854, p=0.002). Tumor size was also analyzed as a continuous variable in multivariate analysis, and CSS decreased with decreasing tumor size (HR 0.919, 95% CI 0.873–0.968, p<0.001). No significant association between tumor size and CSS was observed in patients with T4N0-2M0 MAC of the colon.*

Conclusion: *Smaller tumor size is associated with poorer CSS in patients with T4N0-2M0 MAC of the colon.*

Key words: *colon cancer, mucinous adenocarcinoma, survival, T4 stage, tumor size*

Introduction

Colon cancer, one of the most commonly diagnosed cancers worldwide, affects approximately 1.4 million people and results in more than 693,000 deaths worldwide each year [1,2]. Of all the histological subtypes of colon cancer, MAC accounts for 10-15% and is the second most frequent, next only to adenocarcinoma [3].

MAC of the colon, characterized by large pools of extracellular mucin in more than 50% of the tumor [4], is a distinct biological entity in terms of tumor progression and metastasis [5-7]. Many studies have indicated that MAC of the colon and rectum is correlated with poor biological behavior, including large tumor size [8,9], lymph node involvement, serosal infiltration, and adjacent organ invasion [10,11]. In addition, MAC of the colon and rectum is also reported in more cases of advanced TNM stage [8,10] and responds poorly to first-line chemotherapy [12,13]. In a large population-based study [14], a significantly poorer survival was reported for MAC of rectum than for adenocarcinoma of rectum. Although the

Correspondence to: Sanjun Cai, MD, PhD. Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, 270 Dong'an Road, Shanghai 20032, People's Republic of China. Tel: +86 13661824237, Fax: +86 21 6417 4774, E-mail: csjfuscc@163.com
Received: 12/05/2016; Accepted: 26/05/2016

depth of primary tumor invasion is an important prognostic factor in colon cancer, it may be difficult to identify the depth of tumor invasion in MAC when a mucin pool is present without tumor cells. Therefore, the prognostic role of tumor size, which is significantly associated with MAC, should be further discussed in MAC of the colon.

Smaller tumor size is generally associated with better CSS in patients with colon cancer [15-17]. In several studies, it has been proposed that tumor size can be a useful addition to the TNM staging system for the sake of higher prognostic accuracy in colorectal cancer (CRC) [17-19]. Analyses of different subgroups of colon cancer data, however, have produced some interesting results. In a study of 610 Japanese colon cancer patients, researchers found CSS to be lower with smaller tumors: patients with tumors between 4 and 8 cm in size showed an HR of 0.45 (95% CI 0.293-0.696, p<0.001) relative to patients with tumors <4 cm [20]. Some investigators found that smaller tumors (median 30 mm) did not entail better survival outcomes compared with medium-sized tumors (median 45 mm) or larger tumors (median 60 mm) in patients with non-metastatic CRC (p=0.998) [21].

We hypothesized that small tumor size would reflect a biologically more aggressive phenotype and thus poorer CSS in patients with MAC of the colon with heavy depth of tumor invasion (T4N0-2) without distal metastasis (M0). To test this hypothesis, we analyzed a subset of patients with MAC of the colon with T4N0-2M0 disease from the US Surveillance, Epidemiology, and End Results (SEER) database. We also carried out a preliminary analysis of patients with T4N0-2M0 adenocarcinoma of the colon from the SEER database.

Methods

Selection of T4N0-2M0 MAC of colon patients

The SEER program (http://seer.cancer.gov/), sponsored by the National Cancer Institute, is a population-based cancer registry collecting and publishing cancer incidence and survival data. It comprises 18 population-based cancer registries that cover approximately 26% of the US population. Cases of invasive MAC of the colon from January 1988 to December 2003 were extracted from the database (http://seer.cancer.gov, April 2013 release). Cases that met the following criteria were included: mucinous adenocarcinoma of the colon, age at diagnosis between 18 and 75 years, Caucasian, known depth of invasion and lymph node status, at least 12 retrieved lymph nodes, colon cancer surgically resected with a pathology specimen, pathologically confirmed diagnosis, AJCC stage T4, non-metastatic, known survival time and cause of death, and colon cancer as the only malignant tumor. Patients were excluded if they had undergone neoadjuvant chemoradiotherapy or had only local tumor excision. The Fudan University Shanghai Cancer Center Ethics Committee and Institutional Review Board reviewed and approved the research protocol.

Selection of patients with T4N0-2M0 adenocarcinoma of the colon

We also extracted patients with invasive adenocarcinoma of the colon from the SEER database. The inclusion and exclusion criteria were identical to those in the data selection of T4N0-2M0 MAC of the colon patients.

Outcome measures

The following data were collected from the SEER database: sex, race, age at diagnosis (with 60 years applied as the cutoff in analyses), year of diagnosis, tumor size, pathology grade, histological type, number of primaries, number of lymph nodes harvested (with 18 applied as the cutoff in analyses), number of positive lymph nodes (N0, N1 or N2), depth of local tumor invasion, AJCC TNM stage, radiation sequence with surgery, follow-up time, and SEER cause-specific death classification. All cases were restaged according to the latest AJCC cancer staging manual (7th edition, 2010) [16]. Tumor size was defined as the maximal tumor diameter obtained from pathology reports on resected cancer specimens. The cutoff point for tumor size to differentiate the high- and low-risk groups was identified using X-tile software [22]. In the X-tile software, data are displayed in the x-axis where each point reflects a potential cutoff point. The intensity of the color of the grid represents the strength of the association between tumor size and CSS. The primary end point for our study was CSS, which was calculated from the time of diagnosis to the time of colon cancer-specific death. Deaths attributed to colon cancer were treated as events, and deaths from other causes or being alive at the last follow-up were treated as censored observations.

Statistics

The cutoff value for tumor size was identified based on the X-tile software (http://www.tissuearray.org/rimmlab/) by the minimum p values from log-rank chi-square statistics. Clinicopathological data based on tumor size (using the cutoff value determined with the X-tile software) were summarized using cross-tabulation, and the distributions were compared using chi-square tests. Survival curves were constructed using Kaplan-Meier analysis, and the log-rank test was used to identify differences. Multivariate Cox proportional

Table 1. Demographic characteristics of patients with T4N0-2M0 mucinous adenocarcinoma of colon, stratified by tumor size

Characteristics	*Total (N=585) N (%)*	*Tumor size (cm)* ≤5 cm (N=193) N (%)	>5 cm (N=392) N (%)	*p value*
Median follow-up (mo)	70	55	82	
Sex				0.144
Male	301 (51.5)	91 (47.2)	210 (53.6)	
Female	284 (48.5)	102 (52.8)	182 (46.4)	
Age at diagnosis (years)				0.609
≤60	261 (44.6)	89 (46.1)	172 (43.9)	
>60	324 (55.4)	104 (53.9)	220 (56.1)	
Year of diagnosis				0.804
1988-1996	193 (33.0)	65 (33.7)	128 (32.7)	
1997-2003	392 (67.0)	128 (66.3)	264 (67.3)	
Primary site				0.971
Right colon	434 (74.2)	143 (74.1)	291 (74.2)	
Left colon	151 (25.8)	50 (25.9)	101 (25.8)	
Pathology grade				0.355
High	57 (9.7)	14 (7.0)	43 (11.1)	
Moderate	369 (62.9)	132 (66.3)	237 (61.1)	
Poor	156 (26.5)	52 (26.2)	104 (26.8)	
Undifferentiated	5 (0.9)	1 (0.5)	4 (1.0)	
LNH				0.279
≤18	327 (55.9)	114 (59.1)	213 (54.3)	
>18	258 (44.1)	79 (40.9)	179 (45.7)	
T stage				<0.001
T4a	294 (50.3)	120 (62.2)	174 (44.4)	
T4b	291 (49.7)	73 (37.8)	218 (55.6)	
N stage				0.007
N0	261 (44.6)	72 (37.3)	189 (48.2)	
N1	150 (25.6)	64 (33.2)	86 (21.9)	
N2	174 (29.7)	57 (29.5)	117 (29.8)	

LNH: number of lymph nodes harvested

hazards models were performed to analyze risk factors for survival outcome. Tumor size was also analyzed as a continuous variable in multivariate analysis. All computed p values were two-sided, and statistical significance was accepted at $p<0.05$. All statistical analyses were performed with the SPSS 20.0 statistical package for Windows.

Results

Descriptive statistics in T4 MAC of the colon

A total of 585 patients (301 men and 284 women) in the SEER database were included in the final analysis, of whom 280 (47.9%) were recorded as having died from colon cancer. Patient demographics and pathologic features based on tumor size are shown in Table 1. The median follow-up time was 70 months (interquartile range, 21–121 months). Among all cases, 434 (74.2%) were primarily located in the right colon, and 151 (25.8%) were in the left colon. There were 426 (72.6%) patients pathologically diagnosed with high or moderate differentiation and 161 (27.4%) with poor differentiation or undifferentiation. As for lymph node status, stage N0 cases were the most common, accounting for 44.6% (261), with stage N1 accounting for 25.6% (150) and stage N2 for 29.7% (174). Compared to patients with tumors >5.0 cm, patients with tumors ≤5.0 cm were more likely to have lymph node metastasis, i.e., N1 or

Table 2. Univariate survival analyses of T4N0-2M0 mucinous adenocarcinoma of the colon according to clinicopathological variables

Variables	*No.*	*5-year CSS (%)*	*p value*
Sex			0.199
Male	301	54.4	
Female	284	60.9	
Age at diagnosis (years)			0.117
≤60	261	60.7	
>60	324	54.9	
Year of diagnosis			0.007
1988-1996	193	63.7	
1997-2003	392	54.6	
Primary site			0.130
Right colon	434	59.8	
Left colon	151	51.0	
Pathology grade			0.003
High	57	78.7	
Moderate	369	58.9	
Poor	156	48.5	
Undifferentiated	5	20.0	
LNH			0.390
≤18	327	55.2	
>18	258	60.4	
T4			<0.001
T4a	294	65.7	
T4b	291	49.5	
N stage			<0.001
N0	261	78.7	
N1a	66	58.4	
N1b	84	56.1	
N2a	67	28.6	
N2b	107	23.4	
Tumor size (cm)			0.034
≤5	193	51.6	
>5	392	60.5	

LNH: number of lymph nodes harvested, CSS: cancer-specific survival

N2 (62.7 vs 51.7%, p=0.007). The distribution of T4N0-2M0 MAC of colon patients according to tumor size is shown in Figure 1.

Tumor size vs CSS in T4 MAC of the colon

Analysis using the X-tile program showed a continuous direct association between increasing tumor size and superior CSS and identified 5.0 cm as the optimal cutoff value (Figure 2). Kaplan-Meier analysis showed that tumors ≤5.0 cm had a poorer CSS than tumors >5.0 cm (p=0.034; Figure 3), and the 5-year CSS rates were 51.6 and 60.5% in patients with tumors ≤5.0 cm and >5.0 cm. Univariate analysis of the entire sample indicated that the year of diagnosis (p=0.007), pathology grade (p=0.003), tumor size (p=0.034), N stage (p<0.001), and T stage (p<0.001) were risk factors for CSS (Table 2). An analysis using the multivariate Cox proportional model identified the following independent prognostic factors: tumor size (p=0.002), N stage (p<0.001), and T stage (p<0.001). Compared to patients with tumors ≤5.0 cm, patients with tumors >5.0 cm were more likely to have better CSS (HR 0.658, 95% CI 0.506-0.854, p=0.002, Table 3). To avoid the potential influence of selected cutoff values, we further analyzed tumor size as a continuous variable using the multivariate Cox proportional hazards model. CSS decreased with decreasing tumor size (HR 0.919, 95% CI 0.873–0.968, p<0.001). With each centimeter increase in tumor size, the patient's mortality risk would decrease by 8.1%.

Preliminary analyses in T4 adenocarcinoma of colon

We also included patients with T4N0-2M0 adenocarcinoma of the colon from the SEER database (Table 4). Preliminary analysis showed that there was no significant association between tumor size and CSS (Table 5).

Discussion

In general, large tumor size is associated with heavy tumor burden, lymph node involvement and poor survival outcome in colon cancer [23]. However, analyses of particular subgroups have yielded the opposite findings. In a SEER-based study, Wang et al. found that smaller tumors (≤2.5 cm) entailed worse survival outcome compared with medium-sized tumors (2.5-6.0 cm) or larger tumors (>6.0 cm) in patients with stage IIA colon cancer (p=0.014) [24]. Vinayak et al. reported that in stage III colon cancer, patients with the smallest tumors (<5 mm) had higher 10-year colon cancer-specific mortality compared with those with tumors 5-19 mm, 20-39 mm, 40-59 mm, or ≥60 mm in size (53.3% vs 30.1, 37.5, 39.2, and 39.7% ; p<0.05 in all cases) [25].

The results from the current study indicate

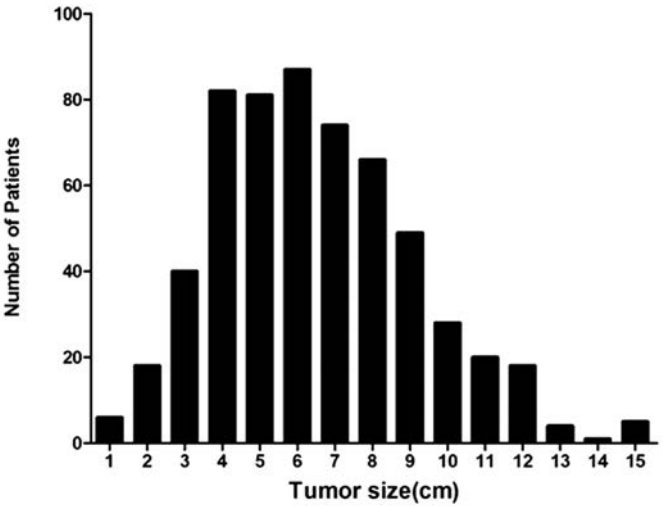

Figure 1. Frequency distribution of T4N0-2M0 MAC of colon patients according to tumor size.

Table 3. Multivariate survival analysis to evaluate the influence of tumor size on CSS in patients with T4N0-2M0 mucinous adenocarcinoma of the colon

Variables	*Multivariate analysis* [a]		*Multivariate analysis* [b]	
	HR (95% CI)	*p value*	*HR (95% CI)*	*p value*
Year of diagnosis		0.145		0.134
1988-1996	reference		reference	
1997-2003	1.231 (0.931-1.628)		1.239 (0.937-1.638)	
Pathology grade		0.102		0.104
High	reference		reference	
Moderate	1.549 (0.978-2.452)		1.511 (0.954-2.392)	
Poor	1.565 (0.947-2.588)		1.521 (0.919-2.516)	
Undifferentiated	3.534 (1.163-10.738)		3.640 (1.201-11.034)	
T stage		<0.001		<0.001
T4a	reference		reference	
T4b	1.711 (1.323-2.214)		1.758 (1.356-2.280)	
N stage		<0.001		<0.001
N0	reference		reference	
N1a	2.003 (1.293-3.102)		2.066 (1.334-3.199)	
N1b	1.940 (1.323-2.214)		1.956 (1.308-2.925)	
N2a	4.345 (2.952-6.394)		4.343 (2.950-6.394)	
N2b	5.415 (3.810-7.696)		5.358 (3.770-7.614)	
Tumor size (cm)[a]		0.002		
≤5	reference		–	
>5	0.658 (0.506-0.854)			
Tumor size (cm)[b]	–		0.919 (0.873-0.968)	0.001

CSS: cancer-specific survival, HR: hazard ratio, CI: confidence interval, [a] Tumor size as a categorical variable, [b] Tumor size as a continuous variable

Table 4. Demographics of patients with T4N0-2M0 adenocarcinoma of the colon

Demographics	*N*	*%*
Median follow-up (mo)	76	
Sex		
Male	1219	48.3
Female	1305	51.7
Age at diagnosis (years)		
≤60	1023	40.5
>60	1501	59.5
Year of diagnosis		
1988-1996	1011	40.1
1997-2003	1513	59.9
Primary site		
Right colon	1593	63.1
Left colon	931	36.9
Pathology grade		
High	150	5.9
Moderate	1595	63.2
Poor	751	29.8
Undifferentiated	28	1.1
LNH		
≤18	1440	57.1
>18	1084	42.9
T stage		
T4a	1466	58.1
T4b	1058	41.9
N stage		
N0	1123	44.5
N1	678	26.9
N2	723	28.6

LNH: number of lymph nodes harvested

that in patients with T4N0-2M0 MAC of the colon, small tumor size is associated with poor survival, as well as with lymph node metastasis. As some researchers have suggested, tumors that reach the serosa and beyond with small size may reflect a vertical growth pattern and early-acquired metastatic potential, whereas tumors that grow to a larger size without distant metastasis may represent a biologically indolent nature and limited metastatic ability [24,26]. These results may support our hypothesis that patients with small tumor size in MAC of the colon with heavy intestinal wall invasion likely reflect a biologically more aggressive phenotype. The fact that surgeons are more likely to treat large tumors more aggressively may help explain our observed associations. A study showed that multivisceral resection is associated with increased tumor size in locally advanced CRC [21]. In addition, Sugarbaker et al. indicated that extracellular mucin would help the tumor cells penetrate into the peritoneal cavity or propel into the lymphatic system in mucinous CRC [27]. This may explain why we failed to identify a significant association between tumor size and CSS in patients with T4N0-2M0 adenocarcinoma of the colon.

Based on our findings, we recommend more

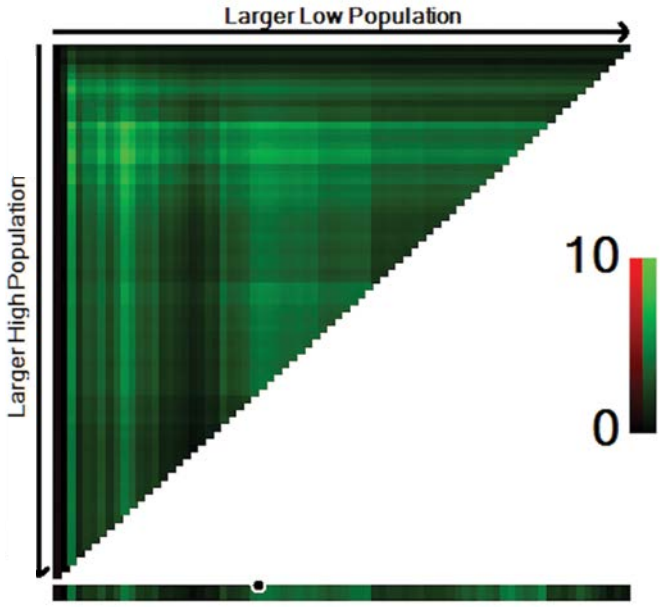

Figure 2. X-tile plots of tumor size in patients with T4N0-2M0 MAC of the colon. The x-axis represents all potential tumor size cutoffs from left to right (low to high) that could be used to define the high and low subsets. Brighter pixels indicate a stronger association between tumor size and CSS. The plot shows the brightest pixels (marked by the black circle) when the entire sample was divided into high and low subsets using a cutoff point of 5.0 cm. Green coloration suggests a continuous direct association between increasing tumor size and greater CSS.

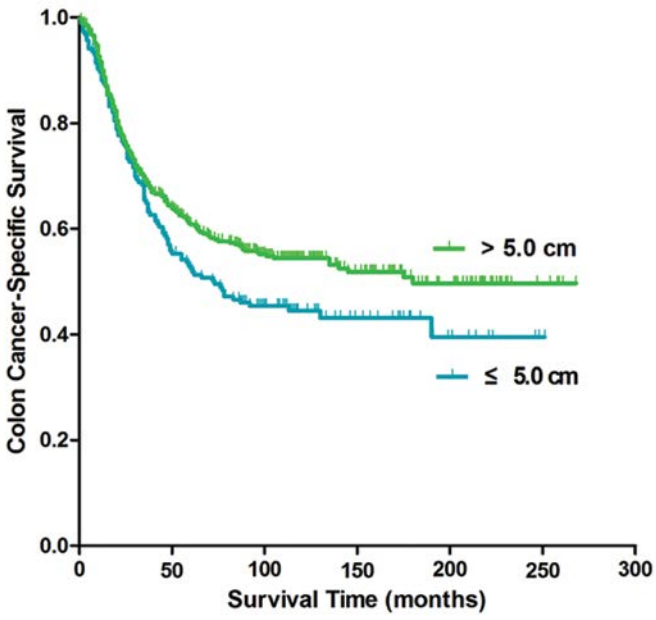

Figure 3. Kaplan-Meier survival curve for patients with T4N0-2M0 MAC of the colon stratified by tumor size (p=0.034).

aggressive excision in MAC of the colon patients with T4N0-2M0 disease whose tumors are small. Especially when the tumor directly invades or is adherent to other organs or structures (T4b), a multivisceral resection is suggested, even though this procedure is correlated with increased incidence of a wide variety of complications [28-30]. Although a minimum of 12 lymph nodes examined in CRC is currently recommended by AJCC [31], many studies suggested a higher threshold for number of retrieved lymph nodes [32,33]. The association between more lymph nodes harvested and greater survival was observed in both stage II [34] and stage III [35] colon cancer. Considering the association between lymph node metastasis and small tumor size, an increase in the number and extent of the retrieved lymph nodes may be recommended for those patients with small tumor size. Intraoperative radiotherapy (IORT), defined as the direct administration of radiation to the tumor bed during surgery, was recommended in the National Comprehensive Cancer Network (NCCN) guidelines as an additional boost for patients with T4 CRC [36]. This type of highly concentrated and precisely targeted radiation not only maximizes the therapeutic effect on microscopic tumor cells but also spares healthy tissues and organs. A systematic review and a meta-analysis confirmed that IORT, as a part of multimodal therapy for locally advanced CRC, could reduce the incidence of local recurrence by over 10% and improve disease-free survival (DFS) and overall survival (OS), when compared to conventional treatment (surgery plus pre-/post-operative therapy) [37,38]. The association between small tumor size and poor survival

Table 5. Univariate analyses to explore the influence of different tumor size cutoffs on CSS in patients with T4N0-2M0 adenocarcinoma of the colon

Tumor size (cm)	*N*	*5-year CSS (%)*	*p value*
≤2	80	63.3	0.722
>2	2444	59.6	
≤3	271	58.9	0.803
>3	2253	59.9	
≤4	717	56.9	0.382
>4	1807	60.5	
≤5	1213	58.1	0.282
>5	1311	61.3	
≤6	1615	58.8	0.295
>6	909	61.4	
≤7	1897	59.5	0.867
>7	627	60.6	
≤8	2110	59.7	0.741
>8	414	59.7	
≤9	2252	59.9	0.237
>9	272	58.2	
≤10	2363	59.7	0.666
>10	161	59.5	

CSS: cancer-specific survival

has led us to recommend IORT in patients with MAC of the colon with T4N0-2M0 disease whose tumors are small despite the wound-associated complications reported in post-IORT patients [38].

To our knowledge, this is the only study to date that focuses on the association between tumor size and CSS in patients with T4N0-2M0 MAC of the colon. The large sample of 585 patients from the SEER database ensures adequate power in the relationship between tumor size and CSS, and therefore, our findings have good reliability. We also analyzed tumor size as a continuous variable and thus circumvented issues that may arise in categorization, such as loss of information, decreased statistical power and poorly controlled confounding effects [39,40]. However, there are still several limitations in our study. Some important patient- and disease-related information cannot be obtained from the SEER database, such as intestinal obstruction or penetration, comorbidities, surgical margin status, lymphovascular or perineural invasion, and data on adjuvant chemotherapy. This clinicopathological information may be a valuable addition to our current analysis. Moreover, our analysis only included patients who had undergone surgical resection, and thus, our findings may not apply to cases with unresectable tumors or those who refuse surgical intervention.

Conclusion

In conclusion, our results provide the first evidence that in patients with T4N0-2M0 MAC of the colon, small tumor size is associated with an unfavorable survival compared with large tumor size. Further studies on MAC of the colon patients with T4N0-2M0 disease are expected to uncover potential molecular and genetic mechanisms for our findings.

Acknowledgements

This study was supported by the grant of the National Natural Science Foundation of China (No.81572351). The authors would like to thank SEER program for public access of the database.

Conflict of interests

The authors declare no confict of interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
3. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum 2005;48:1161-1168.
4. Aaltonen LA, Hamilton SR, World Health Organization, International Agency for Research on Cancer, Pathology and genetics of tumours of the digestive system. World Health Organization classification of tumours. Lyon, Oxford: IARC Press, Oxford University Press (distributor) 2000:109.
5. Yamaguchi T, Taniguchi H, Fujita S et al. Clinicopathological characteristics and prognostic factors of advanced colorectal mucinous adenocarcinoma. Histopathology 2012;61:162-169.
6. Debunne H, Ceelen W. Mucinous differentiation in colorectal cancer: molecular, histological and clinical aspects. Acta Chir Belg 2013;113:385-390.
7. Hugen N, van de Velde CJ, de Wilt JH, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol 2014;25:651-657.
8. Park JS, Huh JW, Park YA et al. Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore) 2015;94:e658.
9. Numata M, Shiozawa M, Watanabe T et al. The clinicopathological features of colorectal mucinous adenocarcinoma and a therapeutic strategy for the disease. World J Surg Oncol 2012;10:109.
10. Thota R, Fang X, Subbiah S. Clinicopathological features and survival outcomes of primary signet ring cell and mucinous adenocarcinoma of colon: retrospective analysis of VACCR database. J Gastrointest Oncol 2014;5:18-24.
11. Song W, Wu SJ, He YL et al. Clinicopathologic features and survival of patients with colorectal mucinous, signet-ring cell or non-mucinous adenocarci-

noma: experience at an institution in southern China. Chin Med J (Engl) 2009;122:1486-1491.

12. Catalano V, Loupakis F, Graziano F et al. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. Br J Cancer 2009;100:881-887.
13. Negri FV, Wotherspoon A, Cunningham D, Norman AR, Chong G, Ross PJ. Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. Ann Oncol 2005;16:1305-1310.
14. Hyngstrom JR, Hu CY, Xing Y et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann Surg Oncol 2012;19:2814-2821.
15. Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Langner C. Value of tumor size as a prognostic variable in colorectal cancer: a critical reappraisal. Am J Clin Oncol 2011;34:43-49.
16. Saha S, Shaik M, Johnston G et al. Tumor size predicts long-term survival in colon cancer: an analysis of the National Cancer Data Base. Am J Surg 2015;209:570-574.
17. Moghimi-Dehkordi B, Safaee A, Zali MR. Prognostic factors in 1,138 Iranian colorectal cancer patients. Int J Colorectal Dis 2008;23:683-688.
18. Poritz LS, Sehgal R, Hartnett K, Berg A, Koltun WA. Tumor volume and percent positive lymph nodes as a predictor of 5-year survival in colorectal cancer. Surgery 2011;150:649-655.
19. Balta AZ, Ozdemir Y, Sucullu I et al. Can horizontal diameter of colorectal tumor help predict prognosis? Ulus Cerrahi Derg 2014;30:115-119.
20. Takahashi T, Kato T, Kodaira S et al. Prognostic factors of colorectal cancer. Results of multivariate analysis of curative resection cases with or without adjuvant chemotherapy. Am J Clin Oncol 1996;19:408-415.
21. Crozier JE, McMillan DC, McArdle CS et al. Tumor size is associated with the systemic inflammatory response but not survival in patients with primary operable colorectal cancer. J Gastroenterol Hepatol 2007;22:2288-2291.
22. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252-7259.
23. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-674.
24. Wang Y, Zhuo C, Shi D et al. Unfavorable effect of small tumor size on cause-specific survival in stage IIA colon cancer, a SEER-based study. Int J Colorectal Dis 2015;30:131-137.
25. Muralidhar V, Nipp RD, Ryan DP, Hong TS, Nguyen PL, Wo JY. Association
26. Between Very Small Tumor Size and Increased Cancer-Specific Mortality in Node-Positive Colon Cancer. Dis Colon Rectum 2016;59:187-193.
27. Yu KD, Jiang YZ, Chen S et al. Effect of large tumor size on cancer-specific mortality in node-negative breast cancer. Mayo Clin Proc 2012;87:1171-1180.
28. Sugarbaker PH. Mucinous colorectal carcinoma. J Surg Oncol 2001;77:282-283.
29. Croner RS, Merkel S, Papadopoulos T, Schellerer V, Hohenberger W, Goehl J. Multivisceral resection for colon carcinoma. Dis Colon Rectum 2009;52:1381-1386.
30. Nakafusa Y, Tanaka T, Tanaka M, Kitajima Y, Sato S, Miyazaki K. Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. Dis Colon Rectum 2004;47:2055-2063.
31. Park S, Lee YS. Analysis of the prognostic effectiveness of a multivisceral resection for locally advanced colorectal cancer. J Korean Soc Coloproctol 2011;27:21-26.
32. Edge SB, American Joint Committee on Cancer, AJCC Cancer Staging Manual (7th Edn), 2010, New York ; London: Springer. xiv, p 648.
33. Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. Am J Surg Pathol 2002;26:179-189.
34. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10:65-71.
35. Sarli L, Bader G, Iusco D et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. Eur J Cancer 2005;41:272-279.
36. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. Ann Surg 2006;244:602-610.
37. Engstrom PF, Arnoletti JP, Benson AB, 3rd et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw 2009;7:778-831.
38. Cantero-Munoz P, Urien MA, Ruano-Ravina A. Efficacy and safety of intraoperative radiotherapy in colorectal cancer: a systematic review. Cancer Lett 2011;306:121-133.
39. Mirnezami R, Chang GJ, Das P et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surg Oncol 2013;22:22-35.
40. Dawson NV, Weiss R. Dichotomizing continuous variables in statistical analysis: a practice to avoid. Med Decis Making 2012;32:225-226.
41. Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. AJNR Am J Neuroradiol 2011;32:437-440.