Clinicopathological characteristics and prognosis of colorectal mucinous adenocarcinoma and nonmucinous adenocarcinoma: a surveillance, epidemiology, and end results (SEER) population-based study

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Background: Mucinous adenocarcinoma (MC) is a rare histological subtype of colorectal adenocarcinoma. Previous studies investigating the prognosis of MC have conflicting results and the proper treatment of MC remains unclear.

Methods: This retrospective study presents the clinicopathological characteristics and prognosis of MC. This cohort study collected data from April 1 through August 01, 2018. This study used data on 107,735 patients with nonmucinous adenocarcinoma (NMC) and 9,494 with MC between 2009 and 2013 from the Surveillance, Epidemiology, and End Results program (SEER). Clinicopathological features were analyzed by chi-square test and survival curves by the Kaplan-Meier method. We used propensity score matching (PSM) to account for potential bias. Logistic regression and Cox proportional hazards models were used to compare and calculate adjusted risks of MC death.

Results: MC was more frequent in patients with older age, large tumor size and moderate tumor grade compared with NMC (P<0.001). Five-year survival was lower for MC patients than NMC patients (P<0.001). Older age, later tumor node metastasis (TNM) stage and multiple tumors indicated a poorer prognosis while surgery gave better survival outcomes [hazard ratio (HR) =0.38; 95% confidence interval (CI), 0.33 to 0.44; P<0.001]. Younger age, left-side colon location and early disease stage were associated with better survival after surgery (P<0.001).

Conclusions: Age, TNM stage, tumor number and treatment were indicators of prognosis and surgery gave better survival for MC patients compared with those without surgery. Our study contributes to their clinical treatment.

Keywords: Colorectal cancer (CRC); mucinous adenocarcinoma (MC); prognosis factor; treatments

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Introduction

Colorectal cancer (CRC) is the fourth leading cause of cancer mortality with approximately 700,000 deaths estimated in 2012 (1). CRC is also the third most commonly diagnosed cancer (2-4). Among CRC subtypes, mucinous adenocarcinoma (MC) is a rare morphologic type in which more than half of tumors are composed of mucin (3,5). In addition, MC might arise from different types of carcinogenesis (6). However, the conclusion about the clinicopathological characteristics of MC is controversial. Some research found that MC patients presented with more advanced disease stage and may have a higher incidence of local extension leading to lower curative and overall resection rates (7,8). While some argued that MC histology may not be associated with greater malignant behavior (9-11) and MC may show better overall survival (OS) (12,13). Therefore, it is crucial to know the clinicopathological characteristics of MC and find out the prognosis factors of MC further.

For treatment of colorectal cancer, almost all patients choose cancer-directed surgical resection (14,15). For MC patients, apart from surgery, few studies reported other treatments for MC such as radiation therapy and chemotherapy: neoadjuvant radiochemotherapy was shown to be a standardized preoperative treatment for selected patients with rectal cancer (16,17); postoperative radiotherapy should be routinely applied to patients with stage II rectal MC (18); MC appeared to be less responsive to fluoropyrimidines, irinotecan and oxaliplatin-based chemotherapy (19). Actually, there was no credible guideline existing for CRC to treat different phenotypes such as MC, so it was quite necessary for us to perform a more intensive subgroup study on the factor of therapy.

Our population-based study systematically summarized the clinicopathological characteristics, prognosis factors of MC versus NMC patients. Meanwhile, we focus on figuring out favorable therapeutic treatments for group of MC patients.

Methods

SEER database

Our data were collected from the Surveillance, Epidemiology, and End Results (SEER) database. SEER is a large, population-based program that collects information about cancer such as incidence, prevalence and survival, covering 28% of the U.S. population (https://seer.cancer.gov/about/overview.html). The SEER program is updated every year and records patient characteristics including age, sex, race, marriage status, disease histological type, stage at diagnosis, tumor size, receipt of surgery, and radiotherapy or chemotherapy.

Patient selection

For a rigorous analysis, colorectal cancer subtypes were defined by the International Classification of Diseases for Oncology (third edition, ICD-O-3) and by TNM classification from the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition. The following inclusion criteria were applied: (I) stage I to IV patients diagnosed with colorectal cancer between 2009 and 2013, and (II) clear histological or microscopical diagnosis and had been classified into different stages according to pathological criteria in AJCC 6th. To further improve the validity and authenticity of our study, patients with unknown survival months, race, tumor size and grade were excluded. Cases without evaluated T stage and with T0 (carcinoma without evidence) or Tis (carcinoma *in situ*) were excluded. Additional exclusion included patients noted death certificate/autopsy or unknown operation. For colonic cancers, colon tumors were subclassified into left-side (distal to the splenic flexure) or right-side (proximal to the splenic flexure) (20). To identify the location of tumors, we did not use SEER codes for tumor location such as appendix C18.1, overlapping lesions of colon C18.8 or colon not otherwise specified (NOS) C18.9. Among 160,805 patients with a diagnosis of stage I to IV colorectal cancer from 2009 to 2013, 117,229 were eligible for potential inclusion into our study according to these selections.

After removing out patients with appendix or peritoneum patients, two other tumor histological subtypes related to MC were in ICD-O-3: mucin-producing adenocarcinoma (code: 8481) and mucinous cystadenocarcinoma (code: 8470). After comparing their prognosis, the former had a similar survival curve to MC and the latter was different so we categorized mucin-producing adenocarcinomas into MC and mucinous cystadenocarcinoma into nonmucinous adenocarcinoma (NMC), assuming that the pathological structure of mucin-producing adenocarcinoma resembled MC. Thus, 9,494 patients were diagnosed with MC (8480: mucinous adenocarcinoma; 8481: mucin-producing adenocarcinoma) and 107,735 NMC (*Figure S1*, Consort diagram).

Statistical analysis

Statistical analyses were by Stata Version 12 (http://www.stata.com) and conducted with R Version 3.4.2 (http://www.R-project.org/). Clinicopathological features were analyzed by chi-square test. Differences between cancer-specific survival (CSS) which means the time from the date of diagnosis to death because of the cancer and OS were analyzed by log-rank test, and survival curves were made by the Kaplan-Meier method. Cox proportional hazard regression models were performed to obtain adjusted hazard ratios (HRs) and 95% confidence interval (CIs) to estimate probable risk factors for survival outcomes. Statistical significance was defined as P less than 0.001. We used Propensity score matching (PSM) to process the analysis with a 1:1 ratio of NMC to MC patients. PSM is a statistical method reduces the impact of treatment-selection bias in estimating treatment effects using observational data (21).

Results

Clinicopathological characteristics of MC patients

To analyze the clinicopathological characteristics of MC patients, we used other adenocarcinoma patients apart from MC (NMC) as a control group. Totally, our study included 107,735 eligible patients with NMC and 9,494 with MC in the SEER database during the 5-year study period [2009–2013]. Descriptive statistics for the study population were in *Table 1*. There were certain differences between NMC patients and MC patients such as patient age, tumor grade, tumor size, tumor number, tumor location, CEA status, AJCC stage and therapy patients received. Among colorectal cancer patients, the ratio of patients older than 65 years old were higher than the younger patients. Meanwhile, the MC groups showed a higher proportion than NMC groups in the patients older than 65 (NMC 56.33% and MC 62.56%, P<0.001), in accordance with the results of Wang *et al.* (5). The major of patients were moderately differentiated (NMC 72.2% and MC 66.88%, P<0.001), MC groups were with poorer differentiation degree compared with NMC groups, since there were more poorly (NMC 16.82% and MC 19.43%, P<0.001) or undifferentiated patients (NMC 3.09% and MC 4.17%, P<0.001). MC groups presented with later tumor stage (AJCC III and IV: NMC 68.82% and MC 78.55%, P<0.001) and larger tumor size (>5 cm: NMC 31.66% and MC 51.07%, P<0.001) in our study population. CEA positivity and right-side colon were more frequently detected in MC groups and always related to higher degree of malignancy (CEA positivity: NMC 25.29% and MC 30.39%, P<0.001; right-side of colon: NMC 46.16% and MC 65.27%, P<0.001). When it comes to the therapy, more MC patients received surgery (NMC 96.39% and MC 98.86%, P<0.001) and more NMC patients may also take radiation into consideration (NMC 11.39% and MC 9.15%, P<0.001).

Survival characteristics of MC patients and NMC patients

Then, we compared 5-year CSS and OS with NMC patients. As shown in the Kaplan-Meier plots (*Figure 1A,B*), MC patients showed lower 5-year CSS rate (NMC: 75.81%, 95% CI, 75.46–76.17%; MC: 70.97%, 95% CI, 69.73–72.22%, P<0.001) and lower 5-year OS rate (NMC: 58.87%, 95% CI, 58.48–59.26%; MC: 51.05%, 95% CI, 49.74–52.39%, P<0.001).

Considering that the sample size was quite different and there were some differences of population baseline characteristics between NMC and MC patients, to avoid these confounding that may made any attribution to the difference of survival between these two groups, we performed PSM with a 1:1 ratio of NMC to MC patients. During PSM, characteristics between the two groups were balanced for gender, race and age, as showed in *Table S1*. After PSM, these matched NMC patients still presented better 5-year CSS rate (NMC: 75.95%, 95% CI, 74.78–77.14%; MC: 70.97%, 95% CI, 69.73–72.22%, P<0.001) and better 5-year OS rate (NMC: 57.67%, 95% CI, 56.37–59.00%; MC: 51.05%, 95% CI, 49.74–52.39%, P<0.001) (*Figure 1C,D*).

Univariate and multivariable survival analysis for MC patients and NMC patients

The univariate Cox regression model was performed to estimate independent prognostic factors of MC patients and NMC patients. The results showed that factors associated with poor survival both in MC and NMC patients were: age at diagnosis more than 65 years, higher tumor grade, positive CEA, larger tumor size, multiple tumors and higher tumor stage (*Tables 2,S2*). However, there are some factors associated with poor survival only in NMC patients, included sex, race and tumor location. All the therapy were protective factors for both group patients, among them, surgery was the most important one (HR =0.23; 95% CI, 0.18–0.28, P<0.001). Through taking all the meaning variables predicted in the univariate Cox regression model

Table 1 Clinicopathological characteristics of patients with NMC or MC

Variable	NMC, n=107,735 (%)	MC, n=9,494 (%)	P
Age (years)			<0.001
≤65	47,043 (43.67)	3,555 (37.44)	
>65	60,692 (56.33)	5,939 (62.56)	
Gender			<0.001
Male	55,402 (51.42)	4,548 (47.9)	
Female	52,333 (48.58)	4,946 (52.1)	
Race			<0.001
White	85,586 (79.44)	7,894 (83.15)	
Black	12,437 (11.54)	983 (10.35)	
Other (American Indian/AK Native, Asian/Pacific Islander)	9,712 (9.01)	617 (6.5)	
Tumor grade			<0.001
Well	8,501 (7.89)	903 (9.51)	
Moderately	77,781 (72.2)	6,350 (66.88)	
Poorly	18,121 (16.82)	1,845 (19.43)	
Undifferentiated	3,332 (3.09)	396 (4.17)	
Tumor size (cm)			<0.001
≤5	73,625 (68.34)	4,645 (48.93)	
>5	34,110 (31.66)	4,849 (51.07)	
Tumor number			
Single	29,418 (27.31)	2,944 (31.01)	
Multiple	78,317 (72.69)	6,550 (68.99)	<0.001
Tumor location			<0.001
Right-side colon	49,732 (46.16)	6,197 (65.27)	
Left-side colon	38,970 (36.17)	2,357 (24.83)	
Rectum	19,033 (17.67)	940 (9.9)	
CEA			<0.001
Negative	36,065 (33.48)	2,816 (29.66)	
Positive	27,245 (25.29)	2,885 (30.39)	
Borderline	345 (0.32)	33 (0.35)	
Unknown	44,080 (40.92)	3,760 (39.6)	
AJCC			<0.001
I, II	33,588 (31.18)	2,036 (21.45)	
III, IV	74,147 (68.82)	7,458 (78.55)	

Table 1 (*continued*)

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Variable	NMC, n=107,735 (%)	MC, n=9,494 (%)	P
Primary tumor (T)			<0.001
T1, T2	28,597 (26.54)	1,314 (13.84)	
T3, T4	79,138 (73.46)	8,180 (86.16)	
Regional lymph nodes (N)			<0.001
N0	61,414 (57)	4,987 (52.53)	
N1, N2	46,321 (43)	4,507 (47.47)	
Distant metastasis (M)			0.004
M0	92,431 (85.79)	8,041 (84.7)	
M1	15,304 (14.21)	1,453 (15.3)	
Surgery			<0.001
No	3,887 (3.61)	108 (1.14)	
Yes	103,848 (96.39)	9,386 (98.86)	
Radiotherapy			<0.001
No radiation and/or cancer-directed surgery	95,464 (88.61)	8,625 (90.85)	
Yes	12,271 (11.39)	869 (9.15)	
Chemotherapy			0.385
No/unknown	66,231 (61.48)	5,793 (61.02)	
Yes	41,504 (38.52)	3,701 (38.98)	

P value of the Chi-square test to compare the NMC and MC groups. NMC, nonmucinous carcinoma; MC, mucinous carcinoma; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.

into the multivariable survival analysis, we found that tumor size (HR =1.07; 95% CI, 1–1.14, P=0.056) and radio therapy (HR =0.98; 95% CI, 0.87–1.12, P=0.807) were no longer independent prognostic factors in MC group patients, but still prognostic factors among NMC patients. While other factors, such as age at diagnosis more than 65 years, positive CEA, higher tumor stage were the most poor independent prognostic factors, and surgery was the most protective factors in both groups (*Tables 2*,*S2*).

Subgroup analyses of different treatments for MC patients

Most of MC patients received surgical treatment no matter which stage they were (*Table 3*), and they benefited a lot from it in general, consistent with previous findings (22,23). As showed in the Kaplan-Meier plots (*Figure 2A*,*B*), MC patients receipted surgery showed much longer 5-year CSS rate (no surgery: 21.57%, 95% CI, 13.35–34.85%; surgery: 70.93%, 95% CI, 69.64–72.24%, P<0.001) and longer 5-year OS rate (no surgery: 9.28%, 95% CI, 4.55–18.92%; surgery: 50.92%, 95% CI, 49.59–52.31%, P<0.001). To avoid other covariates which may affect whether patients receipted surgery or may impact the survival of patients, we performed 1:1 PSM, which included 108 matched patients receipted surgery whose baseline characteristics were well-balanced with patients receipted no surgery. The baseline characteristics after PSM was showed in *Table S3*. After PSM, MC patients receipted surgery still showed better survival (P<0.0001) (*Figure 2C*,*D*).

In clinical practice, we treated different stages patients with different treatments. What's more, it was quite different between treatments of colon and rectal cancer patients, even left colon and right colon cancer were treated as different ones. As a result, we conducted a more intensive subgroup study of different stage or different location on the factor of therapy. According to *Table 3*, we could see that

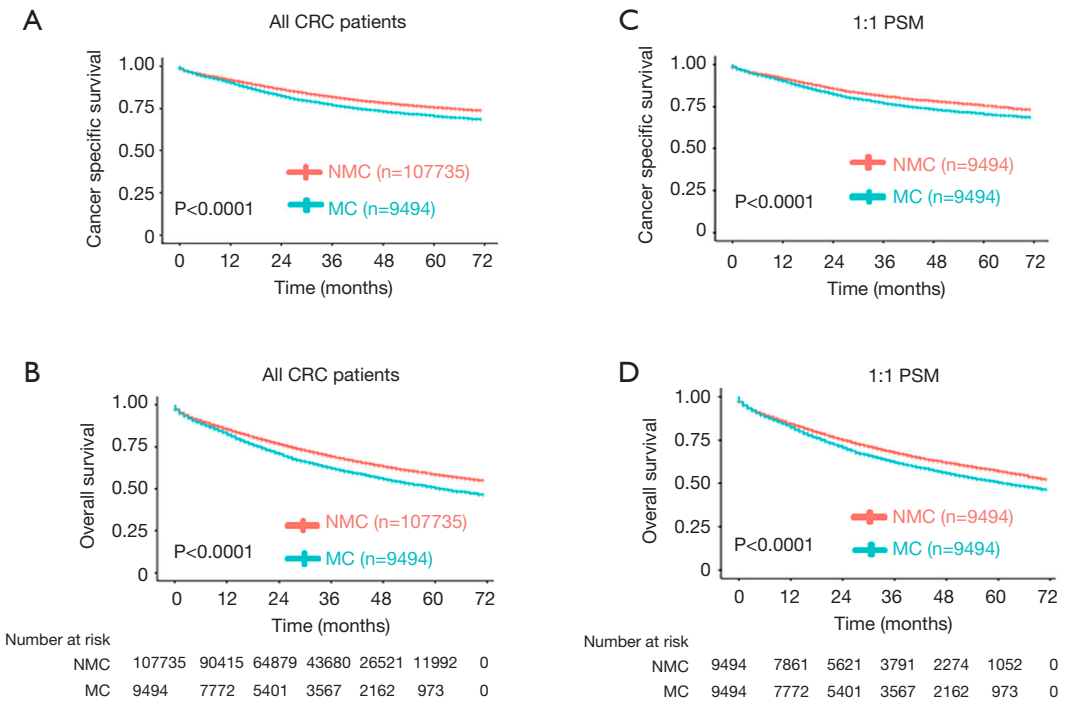

Figure 1 Kaplan-Meier survival estimates for patients with nonmucinous adenocarcinoma (NMC) or mucinous adenocarcinoma (MC). (A) Cancer-specific survival (CSS) for all CRC patients with NMC or MC; (B) Overall survival (OS) for all CRC patients with NMC or MC; (C) CSS after propensity score matching (PSM) for matched patients with NMC or MC; (D) CSS after PSM for matched patients with NMC or MC.

most patients with right colon cancer would receive surgery or surgery combined with chemotherapy, while patients with left colon cancer or rectal cancer would also take radiotherapy into consideration. In the subgroup analysis of right colon cancer patients where Cox's regression models were used to estimate HR and 95% CI for each subgroup, we found that compared with surgery alone, stage II-IV patients would benefit from surgery combined with chemotherapy, while stage I patients wouldn't (*Figure 3A*). The same result was found in the subgroup analysis of left colon cancer patients (*Figure 3B*). However, in the subgroup analysis of rectal cancer patients, surgery combined with chemotherapy was a protective factor just for stage IV patients (*Figure 3C*). Since a small proportion of right colon cancer patients chose radiotherapy, so we performed subgroup analysis of surgery combined with radiotherapy and chemotherapy on left colon cancer patients and rectal patients. The results showed that compared with surgery alone, surgery combined with radiotherapy and chemotherapy improved the prognosis of stage III-IV patients with left colon cancer (*Figure 4A*) and stage II-IV patients with rectal cancer (*Figure 4B*).

Discussion

Previous studies showed that MC was a rare morphologic type of CRC with advanced stage and poor survival (24). To learn more about its clinicopathological features and survival outcomes, we included a large amount of MC patients from SEER database. The result showed that MC patients had specific clinicopathological features compared with other histological type of CRC, including: a higher proportion of patients older than 65 years, poorer differentiation degree, later tumor stage, larger tumor size, a higher rate of CEA positivity and more involvement on right-side of colon. All these features indicated that MC showed higher degree of malignancy. In the survival analysis, we compared 5-year CSS and OS between MC and NMC patients, the result showed that MC presented with poorer survival. And this result still hold after adjusting for confounding factors

Table 2 Univariate and Multivariate Analyses for MC Patients

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
≤65	Ref			Ref		
>65	1.65	1.54–1.77	<0.001	1.63	1.51–1.76	<0.001
Gender						
Female	Ref					
Male	0.98	0.92–1.05	0.623			
Race						
Black	Ref			Ref		
Other	0.83	0.7–0.99	0.037	0.82	0.69–0.97	0.023
White	1.01	0.91–1.13	0.796	0.97	0.87–1.08	0.621
Tumor grade						
Well	Ref			Ref		
Moderately	1.05	0.93–1.18	0.442	1.06	0.94–1.19	0.329
Poorly	1.51	1.33–1.72	<0.001	1.43	1.26–1.63	<0.001
Undifferentiated	1.7	1.43–2.03	<0.001	1.57	1.32–1.88	<0.001
Tumor size (cm)						
≤5	Ref			Ref		
>5	1.23	1.15–1.31	<0.001	1.07	1–1.14	0.056
Tumor number						
Single	Ref			Ref		
Multiple	1.19	1.12–1.28	<0.001	1.11	1.04–1.19	<0.001
Tumor location						
Right-side colon	Ref					
Left-side colon	1.01	0.94–1.09	0.767			
Rectum	0.93	0.83–1.04	0.192			
CEA						
Negative	Ref			Ref		
Positive	2.08	1.9–2.27	<0.001	1.91	1.75–2.08	<0.001
Borderline	1.16	0.62–2.17	0.632	1.12	0.6–2.09	0.724
Unknown	1.56	1.43–1.7	<0.001	1.51	1.38–1.65	<0.001
AJCC						
I, II	Ref			Ref		
III, IV	1.99	1.82–2.18	<0.001	1.99	1.81–2.18	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Surgery						
No	Ref			Ref		
Yes	0.23	0.18–0.28	<0.001	0.2	0.16–0.25	<0.001
Radiotherapy						
No radiation and/or cancer-directed surgery	Ref			Ref		
Yes	0.81	0.72–0.91	<0.001	0.98	0.87–1.12	0.807
Chemotherapy						
No/unknown	Ref			Ref		
Yes	0.92	0.86–0.99	0.018	0.87	0.81–0.94	<0.001

HR, hazard ratio; CI, confidence interval.

Table 3 The number of MC patients with different treatments

AJCC	No treatment	Surgery	Chemotherapy	Surgery radiotherapy	Surgery chemotherapy	Surgery radiotherapy chemotherapy
Right colon						
I	3	800	1	1	13	1
IIa	2	1,833	0	0	169	6
IIb	3	285	1	5	125	20
IIIa	0	62	0	0	71	0
IIIb	4	514	0	1	576	13
IIIc	1	304	0	1	466	10
IV	10	375	12	9	475	26
Left colon						
I	2	255	2	0	6	6
IIa	0	497	0	2	96	31
IIb	0	116	0	4	48	25
IIIa	1	17	0	0	28	3
IIIb	0	182	1	1	217	47
IIIc	0	108	1	2	187	44
IV	7	119	9	3	267	22
Rectal						
I	5	71	1	1	6	37
IIa	2	62	5	12	13	125
IIb	1	13	1	1	4	25
IIIa	0	4	0	1	7	19
IIIb	1	23	4	5	17	165
IIIc	1	28	3	6	22	127
IV	10	16	11	2	24	56

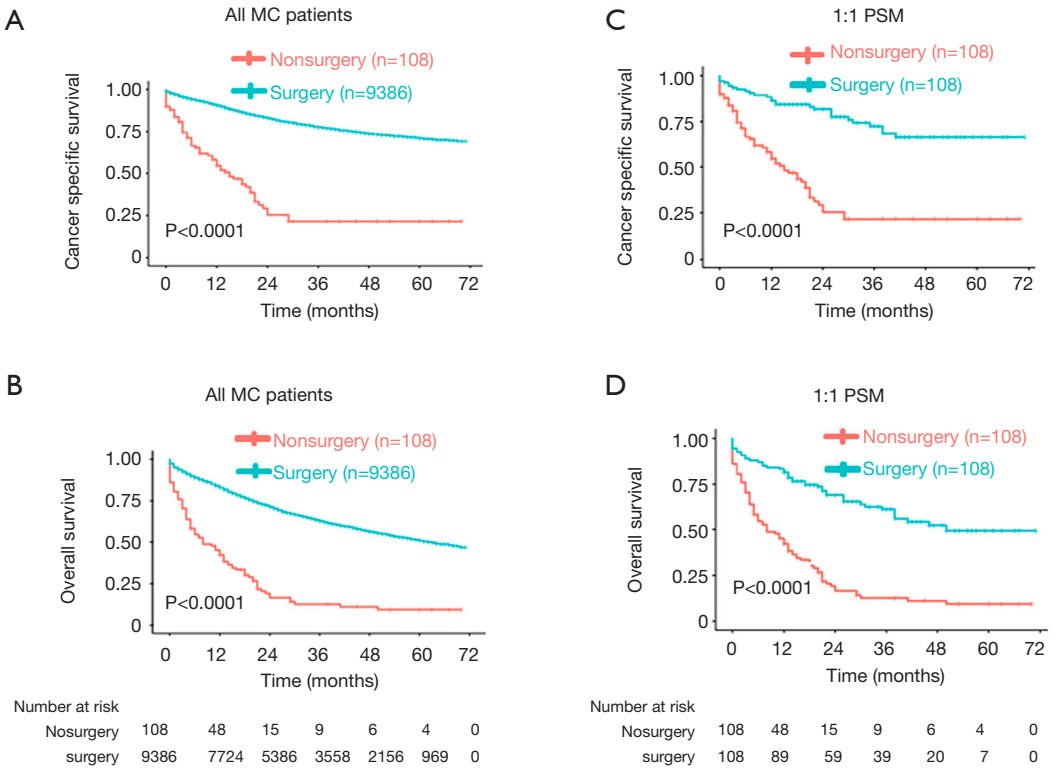

Figure 2 Kaplan-Meier survival estimates for patients with MC with or without therapy. (A) CSS for all MC patients treated with or without surgery; (B) OS for all MC treated with or without surgery; (C) CSS after PSM for matched MC treated with or without surgery; (D) OS after PSM for matched MC treated with or without surgery.

through performing PSM.

Considering that MC patients had poor prognosis, we estimated independent prognostic factors and made a comparation with NMC groups in detail. In a univariate Cox regression model, we found that factors associated with poor survival among MC and NMC patients were: age at diagnosis more than 65 years, higher tumor grade, higher tumor stage, positive CEA, larger tumor size and multiple tumors; at the same time, all the therapy were protective factors for MC and NMC patients, among them, surgery was the most important one. Further more, in the multivariable survival analysis, the result was almost the same, the little difference was tumor size and radiotherapy were no longer prognostic factors in MC groups but they were still prognostic factors among NMC patients.

When it came to the treatment strategies for MC patients, some studies found that standard treatment strategies given to patients with NMC can also be given to patients with MC in accordance with recent guidelines (13). Ott *et al.* suggested the efficacy of common combination chemotherapy protocols for MC patients (25). Considering that no current, credible guidelines exist for treatment of different phenotypes (26), we performed a more intensive subgroup study on the factor of therapy. Nearly all MC patients were recommended to receive surgery which significantly improved OS. Given that multivisceral resection improves OS without increasing short-term mortality (27), appropriate surgery is critical for increasing OS of MC patients. However, there are some limitation since treatments for surgery plan for III and IV stage patients are different. There were limited sample of the latter, who tended to receive the surgery with more consideration of physical condition. Despite the limitation, the present study is significant because surgery is a favorable factor for treatment of different stages MC patients.

Many factors would be included into consideration to recommend suitable treatment strategies for patients, such as tumor characters, general condition of patients, and patients' preference. Apart from surgery, radiotherapy and chemotherapy were both efficient tool for CRC patients as adjuvant preoperative therapies to promote possibility

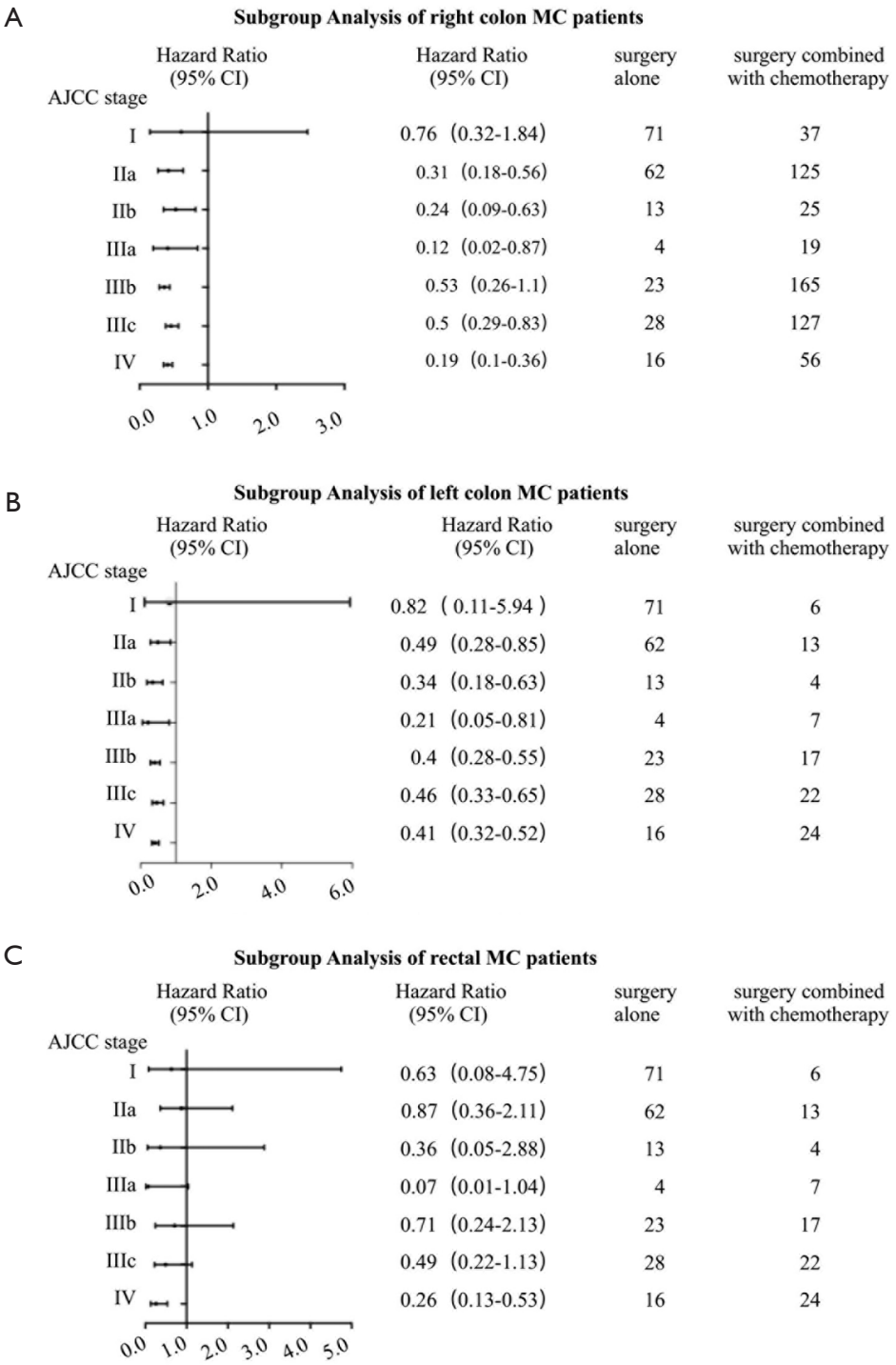

Figure 3 Subgroup analysis. (A) Forest plot of hazard ratios (HRs) of survival for right colon MC patients treated with surgery alone or surgery combined with chemotherapy; (B) Forest plot of hazard ratios (HRs) of survival for left colon MC patients treated with surgery alone or surgery combined with chemotherapy; (C) Forest plot of hazard ratios (HRs) of survival for rectal MC patients treated with surgery alone or surgery combined with chemotherapy.

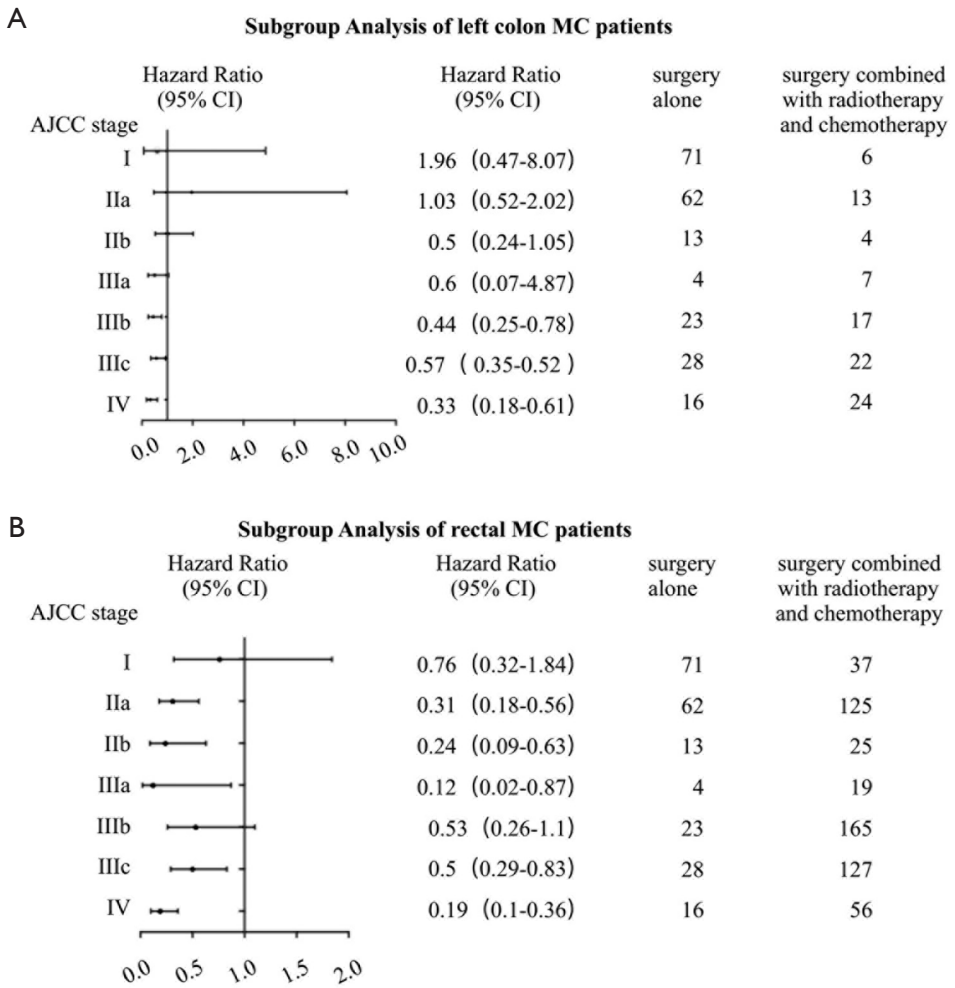

Figure 4 Subgroup analysis. (A) Forest plot of hazard ratios (HRs) of survival for left colon MC patients treated with surgery alone or surgery combined with radiotherapy and chemotherapy; (B) forest plot of hazard ratios (HRs) of survival for rectal MC patients treated with surgery alone or surgery combined with radiotherapy and chemotherapy.

of surgical transformation or as postoperative systemic therapy. But there was no clear guideline on whether these were suitable for MC patients since few studies found that MC patients were not so sensitive to chemotherapy (28-30). Through subgroup analysis, we found that surgery combined with chemotherapy was a better choice compared with surgery alone for stage II–IV colon cancer patients but only for IV rectal cancer patients, which was accordance with some researches' founding that the role of adjuvant chemotherapy was supported for stage II–III colon cancer regardless of the presence of mucinous histology (27). Radiotherapy was more often used in left colon cancer and rectal patients, and we found that the conclusion was quite different: surgery combined with chemotherapy and radiotherapy was more effective for stage II–IV rectal cancer patients but only for IV left colon cancer patients.

The SEER database had completeness and validity of data, but our study had several limitations. First and foremost, SEER did not provide information on details about medication scheme during chemotherapy and radiotherapy, and whether the patient received adjuvant therapy or neoadjuvant therapy was not clear. Second, patient comorbidity was not available so that there would be some confounding factors in the prognosis analysis. What's more, SEER covered about 28% of the total US population and the number of MC cases we studied was relatively small compared with other population-based reports, which may result in selection bias, especially in the part of analysis

of treatments. Meanwhile, the mass data may exist some small aberration, such as the data diagnosed by different pathologists and the pathological reports based on biopsy or surgery or autopsy.

Conclusions

In conclusion, based on our large, population-based, retrospective analysis, MC showed individual clinicopathological characteristics indicating higher degree of malignancy and worse survival. Age, TNM stage, tumor number and treatment were indicators of prognosis. Specific treatment should be made according to the stage and the location of cancer: (I) for stage I colorectal MC patients, surgery was not inferior to other therapy; (II) for stage II–IV colon MC patients, surgery combined with chemotherapy presented with better survival, especially, for stage IV left colon MC patients, surgery combined with chemotherapy and radiotherapy was another choice; (III) for stage II–IV rectal MC patients, surgery combined with chemotherapy and radiotherapy was more effective. We believe that our study may contribute to the treatment of MC patients and continuing efforts are needed to improve proper therapeutic options for them.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The patients in our study were collected from the SEER database, and we received permission for using the data, for non-commercial use.

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Supplementary

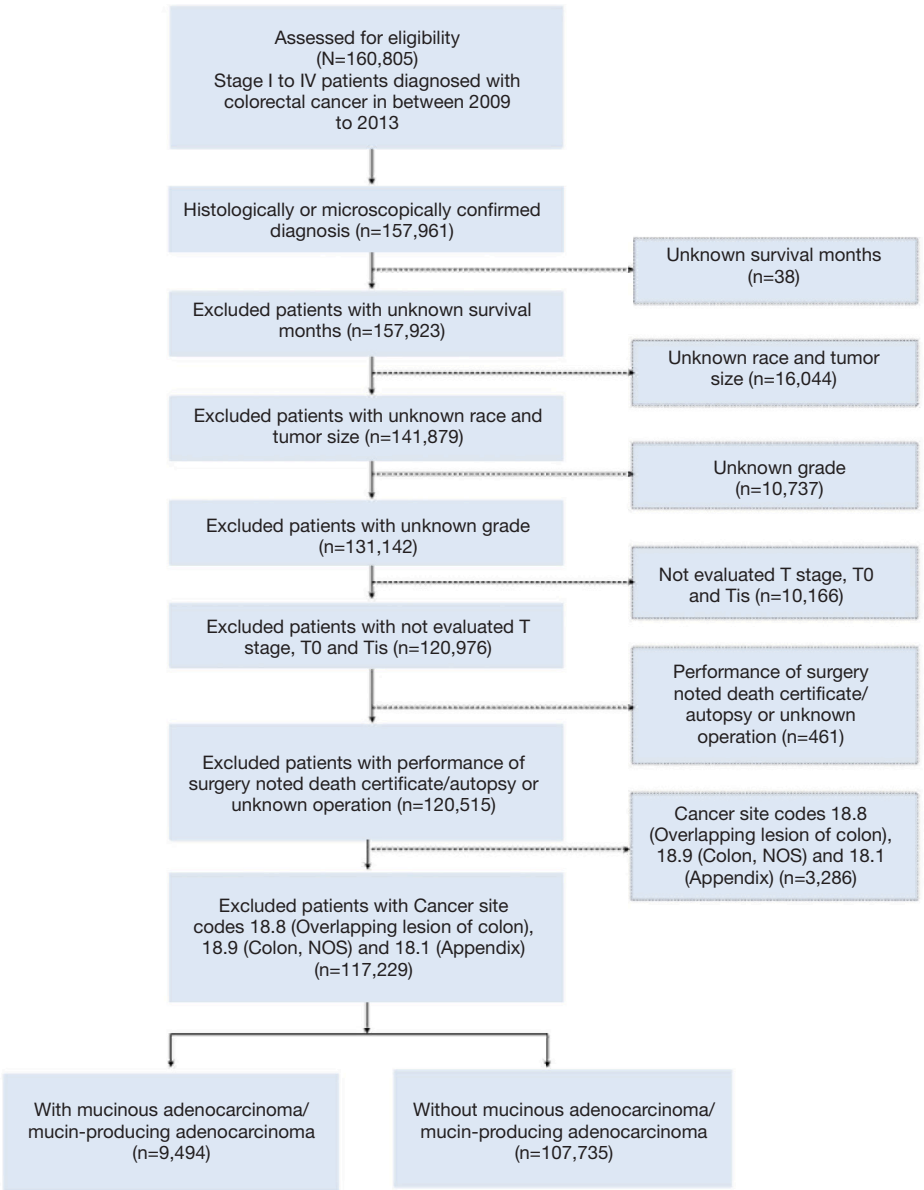

Figure S1 Flow chart for creation of the Surveillance, Epidemiology and End Results (SEER) patient dataset.

Table S1 Clinicopathological characteristics of patients with NMC or MC after PSM

Variable	NMC, n=9,494 (%)	MC, n=9,494 (%)	P
Age (years)			
≤65	3,555 (37.44)	3,555 (37.44)	
>65	5,939 (62.56)	5,939 (62.56)	1
Sex			
Male	4,548 (47.9)	4,548 (47.9)	
Female	4,946 (52.1)	4,946 (52.1)	1
Race			
White	7,894 (83.15)	7,894 (83.15)	
Black	983 (10.35)	983 (10.35)	
Other (American Indian/AK Native, Asian/Pacific Islander)	617 (6.5)	617 (6.5)	1
Tumor grade			
Well	750 (7.9)	903 (9.51)	
Moderately	6,832 (71.96)	6,350 (66.88)	
Poorly	1,626 (17.13)	1,845 (19.43)	
Undifferentiated	286 (3.01)	396 (4.17)	<0.001
Tumor size (cm)			
≤5	6,534 (68.82)	4,645 (48.93)	
>5	2,960 (31.18)	4,849 (51.07)	<0.001
Tumor number			
Single	2,687 (28.3)	2,944 (31.01)	
Multiple	6,807 (71.7)	6,550 (68.99)	<0.001
Tumor location			
Right–side colon	4,533 (47.75)	6,197 (65.27)	
Left–side colon	3,353 (35.32)	2,357 (24.83)	
Rectum	1,608 (16.94)	940 (9.9)	<0.001
CEA			
Negative	3,221 (33.93)	2,816 (29.66)	
Positive	2,373 (24.99)	2,885 (30.39)	
Borderline	29 (0.31)	33 (0.35)	
Unknown	3,871 (40.77)	3,760 (39.6)	<0.001
AJCC			
I, II	2,967 (31.25)	2,036 (21.45)	
III, IV	6,527 (68.75)	7,458 (78.55)	<0.001
Primary tumor (T)			
T1, T2	2,557 (26.93)	1,314 (13.84)	
T3, T4	6,937 (73.07)	8,180 (86.16)	<0.001
Regional lymph nodes (N)			
N0	5,429 (57.18)	4,987 (52.53)	
N1, N2	4,065 (42.82)	4,507 (47.47)	<0.001
Distant metastasis (M)			
M0	8,226 (86.64)	8,041 (84.7)	
M1	1,268 (13.36)	1,453 (15.3)	<0.001
Surgery			
No	330 (3.48)	108 (1.14)	
Yes	9,164 (96.52)	9,386 (98.86)	<0.001
Radiotherapy			
No radiation and/or cancer–directed surgery	8,471 (89.22)	8,625 (90.85)	
Yes	1,023 (10.78)	869 (9.15)	<0.001
Chemotherapy			
No/unknown	6,038 (63.6)	5,793 (61.02)	
Yes	3,456 (36.4)	3,701 (38.98)	<0.001

P value for chi-square tests to compare NMC and MC groups. NMC, nonmucinous carcinoma; MC, mucinous carcinoma; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.

Table S2 Univariate and multivariate analyses for NMC patients

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
≤65	Ref			Ref		
>65	1.94	1.89–1.98	<0.001	1.81	1.77–1.86	<0.001
Sex						
Female	Ref			Ref		
Male	1.05	1.03–1.07	<0.001	1.15	1.12–1.17	<0.001
Race						
Black	Ref			Ref		
Other	0.71	0.67–0.74	<0.001	0.71	0.68–0.75	<0.001
White	0.88	0.85–0.9	<0.001	0.83	0.81–0.86	<0.001
Tumor grade						
Well	Ref			Ref		
Moderately	1.26	1.2–1.32	<0.001	1.11	1.06–1.17	<0.001
Poorly	2.36	2.24–2.47	<0.001	1.83	1.74–1.92	<0.001
Undifferentiated	2.79	2.61–2.98	<0.001	2.14	2–2.29	<0.001
Tumor size (cm)						
≤5	Ref			Ref		
>5	1.58	1.55–1.62	<0.001	1.22	1.19–1.25	<0.001
Tumor number						
Single	Ref			Ref		
Multiple	1.3	1.27–1.33	<0.001	1.16	1.13–1.19	<0.001
Tumor location						
Right-side colon	Ref					
Left-side colon	0.8	0.78–0.82	<0.001	0.96	0.93–0.98	<0.001
Rectum	0.76	0.74–0.78	<0.001	0.96	0.92–0.99	<0.001
CEA						
Negative	Ref			Ref		
Positive	2.48	2.41–2.55	<0.001	2.14	2.08–2.2	<0.001
Borderline	1.3	1.06–1.59	<0.001	1.16	0.95–1.43	<0.001
Unknown	1.58	1.54–1.62	<0.001	1.52	1.48–1.56	<0.001
AJCC						
I, II	Ref			Ref		
III, IV	2.26	2.2–2.32	<0.001	2.16	2.1–2.23	<0.001
Surgery						
No	Ref			Ref		
Yes	0.27	0.26–0.28	<0.001	0.26	0.25–0.28	<0.001
Radiotherapy						
No radiation and/or cancer–directed surgery	Ref			Ref		
Yes	0.59	0.57–0.62	<0.001	0.86	0.82–0.91	<0.001
Chemotherapy						
No/unknown	Ref			Ref		
Yes	0.9	0.88–0.92	<0.001	0.72	0.71–0.74	<0.001

HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.

Table S3 Clinicopathological characteristics of MC patients with or without surgery after PSM

Variable	MC without surgery, n=108 (%)	MC with surgery, n=108 (%)	P
Age (years)			
≤65	56 (51.85)	58 (53.7)	
>65	52 (48.15)	50 (46.3)	0.89
Sex			
Male	70 (64.81)	74 (68.52)	
Female	38 (35.19)	34 (31.48)	0.67
Tumor grade			
Well	10 (9.26)	9 (8.33)	
Moderately	60 (55.56)	68 (62.96)	
Poorly or undifferentiated	38 (35.18)	31 (28.7)	0.47
Tumor size (cm)			
≤5	49 (45.37)	46 (42.59)	
>5	59 (54.63)	62 (57.41)	0.78
Tumor number			
Single	26 (24.07)	31 (28.7)	
Multiple	82 (75.93)	77 (71.3)	0.54
Tumor location			
Right-side colon	36 (33.33)	36 (33.33)	
Left-side colon	24 (22.22)	24 (22.22)	
Rectum	48 (44.44)	48 (44.44)	1.00
AJCC			
I, II	23 (21.3)	21 (19.44)	
III, IV	85 (78.7)	87 (80.56)	0.87
Radiotherapy			
No radiation and/or cancer–directed surgery	104 (96.3)	104 (96.3)	
Yes	4 (3.7)	4 (3.7)	1.00
Chemotherapy			
No/unknown	52 (48.15)	54 (50)	
Yes	56 (51.85)	54 (50)	0.89

P value for chi–square tests to compare NMC and MC groups. NMC, nonmucinous carcinoma; MC, mucinous carcinoma; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.