Original Article

Prognostic implications of mucinous histology in stage III colon cancer with the receipt of adjuvant chemotherapy

Feng Yu[1], Luqiao Huang[1], Feng Shen[1], Shuang Wu[1], Jian Chen[2]

[1]Department of Colorectal Surgery, [2]Department of Gastrointestinal Surgery, Tongde Hospital of Zhejiang Province, Hangzhou, China

Contributions: (I) Conception and design: S Wu, J Chen; (II) Administrative support: F Yu, L Huang; (III) Provision of study materials or patients: F Yu, L Huang, F Shen; (IV) Collection and assembly of data: F Shen, S Wu; (V) Data analysis and interpretation: F Yu, L Huang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jian Chen. Department of Gastrointestinal Surgery, Tongde Hospital of Zhejiang Province, 234 Gucui Road, Hangzhou 310012, China. Email: jimmychen7802@126.com.

Background: There is still a debate about the survival benefit of chemotherapy in stage III mucinous colon cancer, we then conduct a comprehensive assessment of the efficacy of adjuvant chemotherapy in this population.

Methods: The data used in the current study were extracted from the Surveillance, Epidemiology and End Results (SEER) database. Chi-squared (χ^2) test was used to compared patient characteristics according to the histology. The outcome of the survival analysis used in the current study was cancer-specific survival (CSS). Univariable and multivariable analyses were carried out using the Cox proportional hazards regression models to evaluate the prognostic characteristics associated with CSS of colon cancer. And the risks of mortality were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: A total of 68,976 patients diagnosed with stage III colon cancer were included in our analyses, including mucinous adenocarcinoma (MAC, N=6,592) and non-mucinous adenocarcinoma (NMA, N=62,384). In NMA, the receipt of chemotherapy had 46.0% independently decreased risk of colon cancer-specific mortality compared to non-chemotherapy group (HR =0.540, 95% CI: 0.523–0.558, P<0.001). In MAC, the receipt of chemotherapy had 37.7% independently decreased risk of colon cancer-specific mortality compared to non-chemotherapy group (HR =0.623, 95% CI: 0.566–0.685, P<0.001).

Conclusions: MAC was associated with worse prognosis and was less responsive to chemotherapy compared with NMA in stage III colon cancer. However, stage III mucinous colon cancer still need to be treated with chemotherapy because of the significant survival benefit and specialized treatment plans for MAC were quite necessary in the future.

Keywords: Stage III; mucinous; colon cancer; adjuvant chemotherapy; survival

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Introduction

Colon cancer is one of the most frequent types of malignancies in clinical practice (1). As everyone knows that the most common histological type in colon cancer is adenocarcinoma, among which mucinous adenocarcinoma (MAC) is a distinct subtype and consisted of more than 50% extracellular mucin (2). It was reported that MAC occupied 10–20% of colorectal cancer patients, with a lower rate in Asian countries but a higher rate in Western countries (3-7). In addition, MAC was reported to have distinct clinicopathological and genetic features (including advanced stages, microsatellite instability, BRAF mutation, and proximal colon) (7-10).

However, the prognostic value of MAC in colon cancer is still controversial. On the one hand, some researchers believed that MAC was associated with lower survival rate

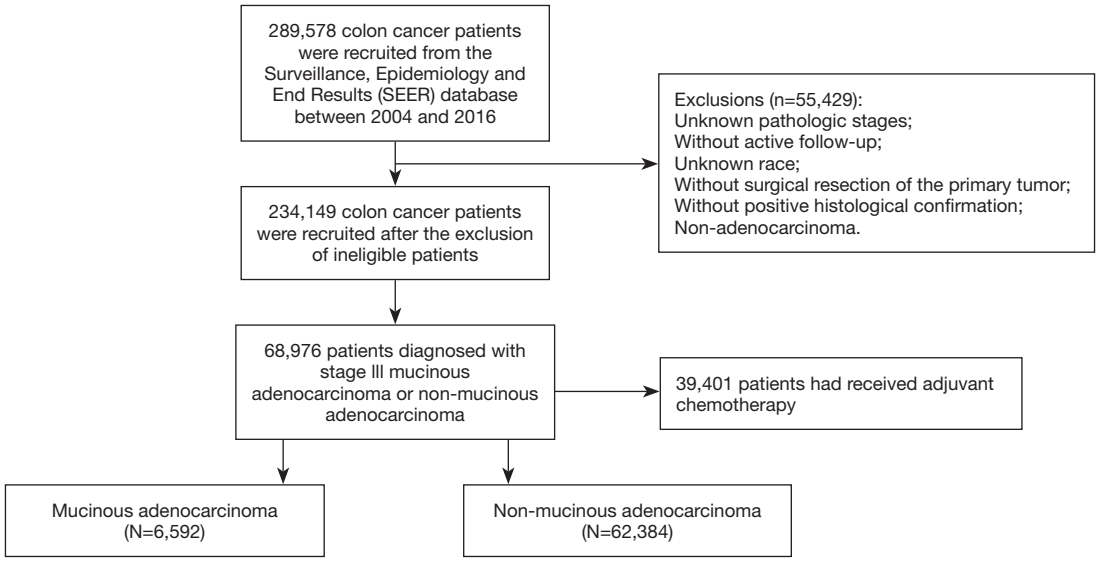

Figure 1 Patient selection flowsheet.

(11,12). On the other hand, others reported that MAC was not independently associated with the prognosis of colon cancer (13).

More importantly, there had been considerable debate with regards to the survival benefit of chemotherapy (CT) in stage III MAC. In stage III colon non-mucinous adenocarcinoma (NMA), the efficacy of adjuvant CT had been confirmed for a long time (14). In stage III mucinous colon cancer, some studies had shown that stage III MAC had worse chemosensitivity as compared with NMA (3,15,16), however, there were also some studies which suggested that there was no significant difference in the survival benefit of adjuvant CT between MAC and NMA (12,17). In addition, National Comprehensive Cancer Network (NCCN) did not take the presence of MAC into consideration when it came to the colon cancer treatment decisions (18).

Moving from this background, we decided to carry out a large population-based study to conduct a comprehensive assessment of the efficacy of adjuvant CT in stage III mucinous colon cancer. Combined with previous findings, we believed our study would add the body of evidence to guide the clinical treatment of stage III mucinous colon cancer.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-160).

Methods

Patients

Given the rarity of mucinous colon cancer, a large cancer database was needed for this study. Sponsored by the US National Cancer Institute and established in 1973, the Surveillance, Epidemiology and End Results (SEER) database was the most authoritative source including the information of cancer incidence, patient survival, clinicopathological features, treatment and outcome data in the United States (https://seer.cancer.gov/). SEER currently collects and publishes cancer-related data annually from SEER-participating areas covering approximately 28% of the U.S. population (19). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This was a study using de-identified data from the SEER database. Ethical approval by the ethical committee of the Tongde Hospital of Zhejiang Province was waived based on our institutional policy. The SEER database is a free database, the data released by the SEER database did not require informed consent of patients.

As shown in *Figure 1*, the data used in the current study were extracted from the SEER database. At first, a total of 289,578 colon cancer patients were recruited between 2004 and 2016. Then, patients meeting the following criteria were excluded from our analyses: (I) unknown pathologic stages; (II) without active follow-up; (III) unknown race;

(IV) without surgical resection of the primary tumor; (V) without positive histological confirmation; (VI) non-adenocarcinoma.

According to the 8th edition of Tumor Node Metastasis (TNM)/American Joint Committee on Cancer (AJCC) staging system, node-negative patients with tumor deposit were restaged as N1. Finally, only patients diagnosed with stage III MAC or NMA were included in our analyses. In the present study, the following variables were identified from the SEER database: T stage, N stage, age, race, gender, tumor location, tumor grade, the receipt of CT and histological subtypes.

Statistical analysis

Chi-squared (χ^2) test was used to compared patient characteristics according to the histology. The outcome of the survival analysis used in the current study was cancer-specific survival (CSS). Survival curves were generated using Kaplan-Meier method for the comparison of CSS difference that was tested using the log-rank test. Univariable and multivariable analyses were carried out using the Cox proportional hazards regression models to evaluate the prognostic characteristics associated with CSS of colon cancer. The risks of mortality were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Variables with P values less than 0.20 in the univariate Cox regression analyses were then included in multivariate regression analyses. In addition, propensity score matching (PSM) was used to provide an estimate of the likelihood that the patient would receive adjuvant CT. A P value less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS, version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Baseline cohort characteristics

As shown in *Figure 1*, a total of 68,976 patients diagnosed with stage III colon cancer were included in our analyses, including MAC (N=6,592) and NMA (N=62,384). The median follow-up time of all the patients was 41 months. Among them, 39,401 (57.1%) patients had received adjuvant CT. The median age of the whole cohort was 69 years, and 48.3% (N=33,314) of them were male. More than a half of the patients were diagnosed with N1 stage (67.2%), and N2 stage only occupied 32.8%.

The demographics and clinicopathological characteristics of all the patients were presented in *Table 1*. MAC was more inclined to be associated with higher T stage (P<0.001), higher N stage (P<0.001), older age (P<0.001), white race (P<0.001), right-side colon cancer (P<0.001) and higher tumor grade (P<0.001), indicating that MAC was correlated with worse clinicopathological features compared with NMA. However, no significant differences were seen between MAC and NMA with regards to gender (P=0.063) and the receipt of CT (P=0.352).

The efficacy of CT in MAC and NMA

First, as shown in *Figure 2A*, we used Kaplan-Meier method to evaluate the survival benefit of CT in the whole cohort, and the survival curves showed that CT group had significantly improved CSS compared with non-CT group (5-year CSS rates: 64.4% *vs.* 77.5%, P<0.0001). For the histological subtypes of colon cancer, NMA group had significantly improved CSS compared with MAC group (5-year CSS rates: 72.7% *vs.* 67.9%, P<0.0001, *Figure 2B*). In addition, the results of Cox analyses also showed that MAC was independently associated with 5.6% increased risk of cancer-specific mortality (HR =1.056, 95% CI: 1.005–1.109, P=0.030, *Table S1*) and the receipt of CT was independently associated with 45.1% decreased risk of colon cancer-specific mortality (HR =0.549, 95% CI: 0.532–0.567, P<0.001, *Table S1*).

We then aimed to evaluate the efficacy of CT in MAC and NMA, respectively. In *Figure 3A*, the receipt of CT was associated with 13.6% increased 5-year CSS rate compared to non-CT group in NMA (5-year CSS rates: 78.1% *vs.* 64.5%, P<0.0001); in MAC, however, the receipt of CT had only 8.2% increased 5-year CSS rate compared to non-CT group (5-year CSS rates: 71.3% *vs.* 63.1%, P<0.0001; *Figure 3B*).

To validate the above results from Kaplan-Meier analyses, variables including T stage, N stage, age, race, gender, tumor location, tumor grade and the receipt of CT were included in univariate Cox proportional hazards regression models, and variables with P values less than 0.20 in the univariate Cox regression analysis were then included in multivariate analyses. In NMA, T stage (P<0.001), N stage (P<0.001), age (P<0.001), race (P<0.001), tumor location (P<0.001), tumor grade (P<0.001) and the receipt of CT (P<0.001) were subsequently incorporated into the multivariate analysis, which showed that the receipt of CT had 46.0% independently decreased risk of colon cancer-

Table 1 Patient characteristics (N=68,976)

Characteristics	Number of patients (%)		P
	Non-mucinous adenocarcinoma (N=62,384)	Mucinous adenocarcinoma (N=6,592)	
T stage			<0.001
T1	3,011 (4.8)	120 (1.8)	
T2	5,586 (9.0)	444 (6.7)	
T3	41,886 (67.1)	4,344 (65.9)	
T4	11,907 (19.1)	1,684 (25.5)	
N stage			<0.001
N1	42,206 (67.7)	4,117 (62.5)	
N2	20,178 (32.3)	2,475 (37.5)	
Age (years)			<0.001
≤65	25,949 (41.6)	2,535 (38.5)	
>65	36,435 (58.4)	4,057 (61.5)	
Race			<0.001
White	48,845 (78.3)	5,439 (82.5)	
Black	7,873 (12.6)	730 (11.1)	
Other	5,666 (9.1)	423 (6.4)	
Gender			0.063
Male	30,202 (48.4)	3,112 (47.2)	
Female	32,182 (51.6)	3,480 (52.8)	
Tumor location			<0.001
Cecum	15,576 (25.0)	2,089 (31.7)	
Ascending colon	12,515 (20.1)	1,706 (25.9)	
Hepatic flexure	3,039 (4.9)	420 (6.4)	
Transverse colon	5,940 (9.5)	717 (10.9)	
Splenic flexure	2,438 (3.9)	242 (3.7)	
Descending colon	4,197 (6.7)	332 (5.0)	
Sigmoid colon	18,679 (29.9)	1,086 (16.5)	
Grade			<0.001
Grade I/II	45,008 (72.1)	4,251 (64.5)	
Grade III/IV	16,389 (26.3)	1,954 (29.6)	
Unknown	987 (1.6)	387 (5.9)	
Chemotherapy			0.352
No/unknown	26,713 (42.8)	2,862 (43.4)	
Yes	35,671 (57.2)	3,730 (56.6)	

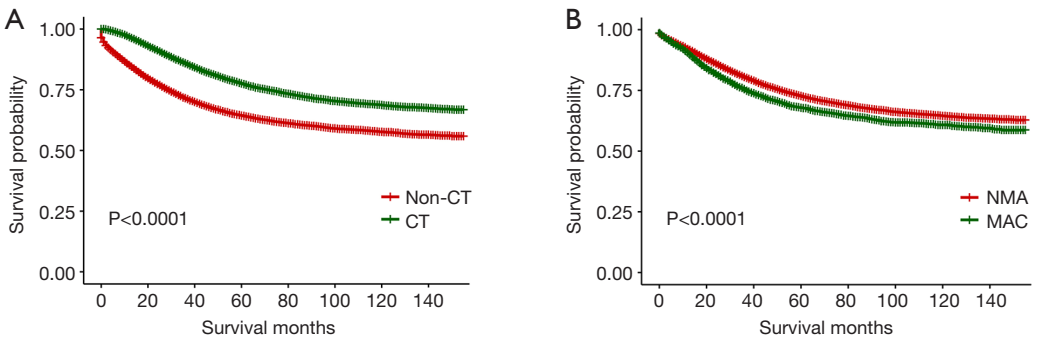

Figure 2 Kaplan-Meier curves of CSS in the whole cohort. (A) Treated with or without adjuvant chemotherapy (CT); (B) MAC or NMA. CSS, cancer-specific survival; MAC, mucinous adenocarcinoma; NMA, non-mucinous adenocarcinoma.

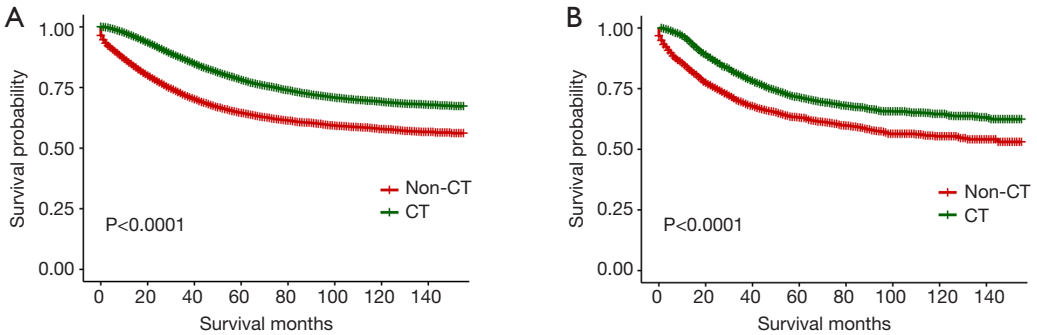

Figure 3 Kaplan-Meier curves of CSS according to the treatment with or without adjuvant chemotherapy. (A) In stage III non-mucinous colon cancer; (B) in stage III mucinous colon cancer. CSS, cancer-specific survival.

specific mortality compared to non-CT group in NMA (HR =0.540, 95% CI: 0.523–0.558, P<0.001, *Table 2*). In addition, higher T stage (P<0.001), higher N stage (P<0.001), older age (P<0.001), black race (P<0.001) and higher tumor grade (P<0.001) were also correlated with increased risk of colon cancer-specific mortality in NMA.

In MAC, T stage (P<0.001), N stage (P<0.001), age (P<0.001), gender (P=0.061), tumor location (P=0.029), tumor grade (P<0.001) and the receipt of CT (P<0.001) were subsequently incorporated into the multivariate analysis, which showed that the receipt of CT had 37.7% independently decreased risk of colon cancer-specific mortality compared to non-CT group (HR =0.623, 95% CI: 0.566–0.685, P<0.001, *Table 3*). In addition, higher T stage (P<0.001), higher N stage (P<0.001), older age (P<0.001), male (P=0.042) and higher tumor grade (P<0.001) were also correlated with increased risk of colon cancer-specific mortality in MAC.

The effect of histological subtype in patients with the receipt of CT

To confirm the above findings about the survival difference in MAC and NMA with the receipt of CT to guide clinical treatment decision, patients with the receipt of CT were recruited for further Cox analyses.

In these patients, T stage (P<0.001), N stage (P<0.001), age (P<0.001), gender (P<0.001), race (P<0.001), tumor location (P<0.001), tumor grade (P<0.001) and histological subtype (P<0.001) were subsequently incorporated into the multivariate analysis, which showed that the MAC was independently associated with 15.4% increased risk of colon cancer-specific mortality compared to NMA (HR =1.154, 95% CI: 1.078–1.235, P<0.001, *Table 4*). Combined with the above results, it was found the increased risk of cancer-specific mortality of MAC compared to NMA was higher in patients with the receipt of CT (15.4%) than in the whole cohort (5.6%).

Table 2 Factors associated with a CCSS in univariate and multivariate analyses in NMA

Variables	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P	HR (95% CI)	P
T stage		<0.001		<0.001
T1	1		1	
T2	1.598 (1.372–1.862)	<0.001	1.441 (1.237–1.679)	<0.001
T3	3.709 (3.248–4.236)	<0.001	3.010 (2.633–3.440)	<0.001
T4	7.926 (6.929–9.068)	<0.001	6.091 (5.317–6.976)	<0.001
N stage		<0.001		<0.001
N1	1		1	
N2	1.990 (1.927–2.005)		1.837 (1.778–1.898)	
Age (years)		<0.001		<0.001
≤65	1		1	
>65	1.600 (1.548–1.654)		1.408 (1.359–1.458)	
Race		<0.001		<0.001
White	1		1	
Black	1.155 (1.103–1.209)	<0.001	1.311 (1.252–1.374)	<0.001
Other	0.898 (0.848–0.951)	<0.001	0.948 (0.895–1.004)	0.069
Gender		0.419		–
Male	1		–	
Female	1.013 (0.981–1.046)		–	
Tumor location		<0.001		<0.001
Cecum	1		1	
Ascending colon	0.830 (0.792–0.869)	<0.001	0.905 (0.864–0.948)	<0.001
Hepatic flexure	0.891 (0.827–0.961)	0.003	1.006 (0.933–1.085)	0.872
Transverse colon	0.820 (0.772–0.871)	<0.001	0.910 (0.856–0.966)	0.002
Splenic flexure	0.839 (0.771–0.913)	<0.001	0.923 (0.848–1.005)	0.064
Descending colon	0.713 (0.665–0.765)	<0.001	0.855 (0.796–0.917)	<0.001
Sigmoid colon	0.670 (0.642–0.699)	<0.001	0.865 (0.828–0.904)	<0.001
Grade		<0.001		<0.001
Grade I/II	1		1	
Grade III/IV	1.563 (1.511–1.617)	<0.001	1.246 (1.204–1.291)	<0.001
Unknown	1.018 (0.892–1.163)	0.790	1.127 (0.986–1.287)	0.079
Chemotherapy		<0.001		<0.001
No/unknown	1		1	
Yes	0.527 (0.510–0.544)		0.540 (0.523–0.558)	

CCSS, colon cancer-specific survival; NMA, non-mucinous adenocarcinoma; HR, hazard ratio; CI, confidence interval.

Table 3 Factors associated with a CCSS in univariate and multivariate analyses in MAC

Variables	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P	HR (95% CI)	P
T stage		<0.001		<0.001
T1	1		1	
T2	0.991 (0.547–1.794)	0.975	1.025 (0.566–1.857)	0.935
T3	2.504 (1.478–4.242)	0.001	2.200 (1.298–3.731)	0.003
T4	5.421 (3.193–9.202)	<0.001	4.610 (2.712–7.837)	<0.001
N stage		<0.001		<0.001
N1	1		1	
N2	2.195 (2.003–2.406)		2.037 (1.855–2.237)	
Age (years)		<0.001		<0.001
≤65	1		1	
>65	1.349 (1.227–1.483)		1.330 (1.203–1.470)	
Race		0.419		–
White	1		–	
Black	1.090 (0.947–1.254)	0.230	–	
Other	1.063 (0.888–1.273)	0.505	–	
Gender		0.061		0.042
Male	1		1	
Female	0.916 (0.836–1.004)		0.908 (0.828–0.996)	
Tumor location		0.029		0.074
Cecum	1		1	
Ascending colon	0.964 (0.855–1.087)	0.551	1.015 (0.899–1.145)	0.811
Hepatic flexure	0.772 (0.623–0.957)	0.018	0.800 (0.645–0.991)	0.041
Transverse colon	0.855 (0.750–1.045)	0.151	0.906 (0.767–1.070)	0.244
Splenic flexure	1.152 (0.917–1.447)	0.224	1.101 (0.875–1.384)	0.412
Descending colon	0.800 (0.630–1.016)	0.067	0.867 (0.682–1.101)	0.242
Sigmoid colon	1.042 (0.911–1.191)	0.550	1.092 (0.954–1.250)	0.203
Grade		<0.001		<0.001
Grade I/II	1		1	
Grade III/IV	1.451 (1.315–1.600)	<0.001	1.215 (1.100–1.343)	<0.001
Unknown	1.395 (1.166–1.670)	<0.001	1.183 (0.988–1.418)	0.068
Chemotherapy		<0.001		<0.001
No/unknown	1		1	
Yes	0.637 (0.581–0.698)		0.623 (0.566–0.685)	

CCSS, colon cancer-specific survival; MAC, mucinous adenocarcinoma; HR, hazard ratio; CI, confidence interval.

Table 4 Factors associated with a CCSS in univariate and multivariate analyses in patients with the receipt of CT

Variables	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P	HR (95% CI)	P
T stage		<0.001		<0.001
T1	1		1	
T2	1.444 (1.175–1.774)	<0.001	1.314 (1.069–1.615)	0.001
T3	3.543 (2.969–4.227)	<0.001	2.810 (2.353–3.357)	<0.001
T4	7.727 (6.461–9.241)	<0.001	5.643 (4.712–6.759)	<0.001
N stage		<0.001		<0.001
N1	1		1	
N2	2.247 (2.153–2.345)		1.943 (1.860–2.029)	
Age (years)		<0.001		<0.001
≤65	1		1	
>65	1.201 (1.151–1.253)		1.221 (1.169–1.275)	
Race		<0.001		<0.001
White	1		1	
Black	1.164 (1.095–1.237)	<0.001	1.278 (1.202–1.359)	<0.001
Other	0.917 (0.850–0.989)	0.025	0.967 (0.896–1.043)	0.382
Gender		<0.001		<0.001
Male	1		1	
Female	0.885 (0.848–0.924)		0.864 (0.827–0.901)	
Tumor location		<0.001		<0.001
Cecum	1		1	
Ascending colon	0.813 (0.763–0.866)	<0.001	0.892 (0.837–0.950)	<0.001
Hepatic flexure	0.927 (0.840–1.024)	0.134	1.026 (0.929–1.132)	0.616
Transverse colon	0.807 (0.743–0.876)	<0.001	0.886 (0.816–0.962)	0.004
Splenic flexure	0.826 (0.737–0.927)	0.001	0.887 (0.791–0.996)	0.042
Descending colon	0.740 (0.674–0.812)	<0.001	0.850 (0.774–0.934)	0.001
Sigmoid colon	0.689 (0.651–0.729)	<0.001	0.832 (0.785–0.882)	<0.001
Grade		<0.001		<0.001
Grade I/II	1		1	
Grade III/IV	1.589 (1.518–1.663)	<0.001	1.279 (1.221–1.341)	<0.001
Unknown	1.274 (1.097–1.480)	0.002	1.273 (1.094–1.480)	0.002
Histology		<0.001		<0.001
Non-mucinous adenocarcinoma	1		1	
Mucinous adenocarcinoma	1.331 (1.245–1.423)		1.154 (1.078–1.235)	

CCSS, colon cancer-specific survival; CT, chemotherapy; HR, hazard ratio; CI, confidence interval.

PSM was also used to investigate the effect of histological subtype in patients with the receipt of CT. In NMA, no significant differences were seen between non-CT and CT groups in all the patient characteristics after PSM (P>0.05, *Table S2*), the receipt of CT was associated with 13.5% increased 5-year CSS rate compared to non-CT group (5-year CSS rates: 76.8% *vs.* 63.3%, P<0.0001; *Figure S1A*); in MAC, no significant differences were seen between non-CT and CT groups in all the patient characteristics after PSM (P>0.05, *Table S3*), however, the receipt of CT had only 8.4% increased 5-year CSS rate compared to non-CT group (5-year CSS rates: 71.0% *vs.* 62.6%, P<0.0001; *Figure S1B*), which were consistent with the above findings.

Discussion

MAC was a rare histological type in colorectal cancer, it was reported to account for 10–20% of colorectal cancer patients. MAC was more common in the female, proximal colon and younger patients, and was more likely to be associated with advanced stages, high-degree microsatellite instability (MSH-H) and BRAF mutations (8,13,20). Compared with the NMA, mucinous colon cancer also had a higher rate of peritoneal implantation and lymph node metastasis, and was characterized by a significantly larger maximal size (21,22).

It was reported that transmembrane mucins and secreted mucins constituted the mucin family of human, and mucins could protect the epithelia by forming a mucus barrier. However, the mucin that gastrointestinal tract synthesized was not a single type, and one certain type of mucin might be dominantly expressed in one organ (23). According to previous research reports, mucin2 and mucin5AC might be related with the occurrence of colon MAC (24). Moreover, recent research showed that MUC2 and MUC5AC may become potential new targets for future treatment strategies of colon MAC in view of the different expression levels of them in MAC and NMA. However, up to now, the carcinogenesis mechanism was not entirely clear behind MUC2 and MUC5AC (13).

In spite of that the different gene expression and histology between NMA and MAC might suggest a different carcinogenesis mechanism, patients with mucinous colon cancer currently received treatments based on the standard treatment regimens of non-mucinous colon cancer and no specific clinical treatment guidelines had been developed for MAC (13,25-28).

In the current study, it was found that MAC was correlated with higher T stage and higher N stage, and was more likely to be found in cecum, ascending colon and hepatic flexure; the Kaplan-Meier survival analyses showed that the 5-year CSS rates of NMA and MAC were 72.7% and 67.9%, respectively. In addition, the results of multivariate Cox analyses confirmed the worse prognosis of MAC when compared with NMA, which showed that MAC was independently associated with 5.6% increased risk of cancer-specific mortality compared with NMA. Few studies focused on the prognostic value of MAC in stage III colon cancer, and one recent research also found that MAC had 5.0% increased risk of mortality compared with NMA in stage III disease, which was similar to our finding (29). Although the survival difference between NMA and MAC achieved statistical difference in the present study, the magnitude of the difference was very small. It was therefore understandable that Catalano *et al*. (12) reported that mucinous histology did not show prognostic difference compared with NMA (P=0.5324) and the sample size of this study was very small with only 178 patients diagnosed with mucinous colon cancer included in this study.

More importantly, our study aimed to evaluate the efficacy of CT according to the histological type. In NMA, it was found that the 5-year CSS rates of CT group and non-CT group were 78.1% and 64.5%, respectively; in MAC, the 5-year CSS rates of CT group and non-CT group were 71.3% and 63.1%, respectively. After adjusting for other prognostic factors, results of multivariate Cox analyses showed that the receipt of CT was independently correlated with 46.0% decreased risk of colon cancer-specific mortality compared with non-CT group in NMA, and this number had fallen to 37.7% in MAC, indicating that MAC patients were less responsive to CT as compared to those with NMA. In addition, as a respective observational work, PSM was used to address potential bias in the present study, and the results also validated the above finding that MAC was less responsive to CT compared with NMA in stage III colon cancer.

To confirm the above findings about the survival difference between MAC and NMA with the receipt of CT to guide clinical treatment decisions, we then furtherly conducted Cox analyses in patients with the receipt of CT, and it was found that MAC was independently associated with 15.4% increased risk of colon cancer-specific mortality as compared with NMA.

Given that MAC was independently associated with only 5.6% increased risk of cancer-specific mortality as compared with NMA in the whole cohort, this result showed that the

survival difference between MAC and NMA was amplified with the receipt of CT. The efficacy of adjuvant CT had been confirmed in stage III NMA, again, it demonstrated that MAC had reduced responsiveness to adjuvant CT, which was in agreement with previous reports (30-32).

However, Hugen and his colleagues (17) reported that the survival difference between MAC and NMA was not statistically significant in stage III disease with the receipt of adjuvant CT. We believed the different result from our study was probably because of the fact that multivariate analyses in their study had taken the rough staging system into account instead of the important T stage and N stage and their analyses were based on old AJCC TNM staging system which might miss N1c disease.

At a molecular level, this poor response of CT in MAC was attributed to the relative hypoxic state owing to a reduction in blood supply, and the histopathologic investigations showed that MAC had less micro-vessel density (MVD) than NMA, which might reduce the chemosensitivity because drug transport were closely related to tumor microcirculation (33-35).

Recently, with the analyses of 16,741 patients with stage III colon MAC, a large population-based study found that MAC with the receipt of CT was associated with 44% decreased risk of mortality as compared with NMA in stage III disease. However, the researchers of this study did not conduct a direct comparison survival benefit offered by CT between MAC and NMA (29).

To the best of our knowledge, aiming to guide clinicians in making treatment decisions in clinical practice, the current study was the first large population-based study to focus on stage III mucinous colon cancer and assess the efficacy of CT in stage III MAC with direct comparison with non-mucinous disease in recent years. Therefore, this study not only added to the body of evidence that the receipt of CT significantly improved the prognosis of stage III mucinous colon cancer, but also confirmed the reduced responsiveness to CT in MAC as compared with NMA. Stage III mucinous colon cancer still need to be treated with CT because of the significant survival benefit under the existing guidelines for colon cancer treatment. More importantly, however, the adjuvant treatment recommendations for stage III colon cancer should take histology into account, there was urgent need to develop individualized treatment programs for mucinous colon cancer in the future.

Two limitations in our analyses still need to be addressed. On the one hand, the SEER database had its inherent shortcomings, the lack of detailed clinicopathological factors including microsatellite instability, BRAF mutation, specific CT regimens, and tumor recurrence that might contribute to further exploration of the prognosis of MAC. On the other hand, it was a retrospective observational study, the biases inherent to the retrospective and non-randomized nature of our analyses could not be completely removed, which might limit the conclusions that had be drawn, and the absence of prospective studies evaluating the efficacy of CT in stage III colon MAC required a cautious interpretation of our results.

In conclusion, MAC had minor worse prognosis and was less responsive to CT compared with NMA in stage III colon cancer. The survival difference was amplified with the receipt of CT. However, stage III mucinous colon cancer still need to be treated with CT because of the significant survival benefit and specialized treatment plans for MAC were quite necessary in the future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-160). 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This was a study using de-identified data from the SEER database. Ethical approval by the ethical committee of the Tongde Hospital of Zhejiang Province was waived based on our institutional policy. The SEER database is a free database, the data released by the SEER database did not require informed consent of patients.

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Supplementary

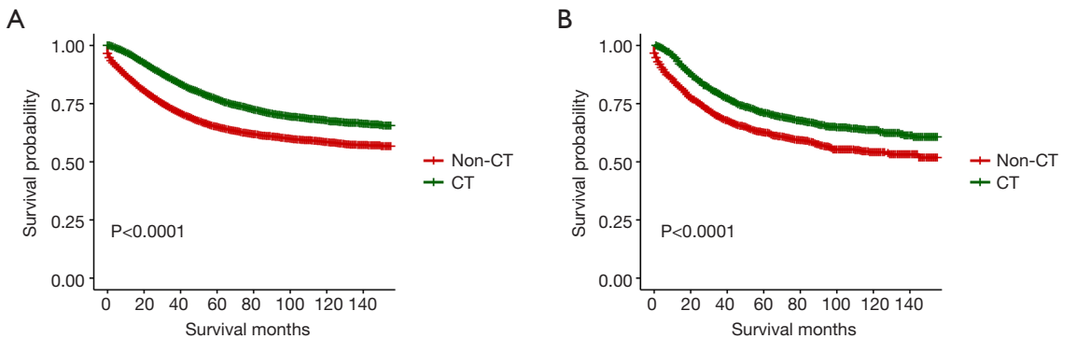

Figure S1 Kaplan-Meier curves of CSS after propensity score matching. (A) In stage III nonmucinous colon cancer; (B) in stage III mucinous colon cancer. CT, chemotherapy.

Table S1 Factors associated with a CCSS in univariate and multivariate analyses in the whole cohort

Variables	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P	HR (95% CI)	P
T stage		<0.001		<0.001
T1	1		1	
T2	1.562 (1.347–1.811)	<0.001	1.419 (1.224–1.645)	<0.001
T3	3.653 (3.212–4.155)	<0.001	2.967 (2.607–3.377)	<0.001
T4	7.845 (6.887–8.937)	<0.001	6.043 (5.300–6.891)	<0.001
N stage		<0.001		<0.001
N1	1		1	
N2	2.017 (1.957–2.078)		1.858 (1.802–1.917)	
Age (years)		<0.001		<0.001
≤65	1		1	
>65	1.574 (1.526–1.624)		1.400 (1.354–1.447)	
Race		<0.001		<0.001
White	1		1	
Black	1.146 (1.097–1.197)	<0.001	1.294 (1.238–1.352)	<0.001
Other	0.905 (0.857–0.956)	<0.001	0.956 (0.905–1.010)	0.112
Gender		0.839		–
Male	1		–	
Female	1.003 (0.973–1.034)		–	
Tumor location		<0.001		<0.001
Cecum	1		1	
Ascending colon	0.846 (0.810–0.883)	<0.001	0.919 (0.880–0.960)	<0.001
Hepatic flexure	0.876 (0.816–0.941)	<0.001	0.979 (0.912–1.051)	0.561
Transverse colon	0.827 (0.781–0.875)	<0.001	0.911 (0.861–.956)	0.001
Splenic flexure	0.868 (0.802–0.939)	<0.001	0.943 (0.871–1.021)	0.147
Descending colon	0.719 (0.672–0.769)	<0.001	0.860 (0.803–0.920)	<0.001
Sigmoid colon	0.688 (0.661–0.717)	<0.001	0.883 (0.847–0.921)	<0.001
Grade		<0.001		<0.001
Grade I/II	1		1	
Grade III/IV	1.556 (1.507–1.607)	<0.001	1.244 (1.204–1.286)	<0.001
Unknown	1.172 (1.055–1.302)	0.003	1.157 (1.040–1.286)	0.007
Histology		<0.001		0.030
Non-mucinous adenocarcinoma	1		1	
Mucinous adenocarcinoma	1.207 (1.150–1.267)		1.056 (1.005–1.109)	
Chemotherapy		<0.001		<0.001
No/unknown	1		1	
Yes	0.538 (0.522–0.554)		0.549 (0.532–0.567)	

CCSS, colon cancer-specific survival; HR, hazard ratio; CI, confidence interval.

Table S2 Patient characteristics in stage III NMA after PSM

Characteristics	Number of patients (%)		P
	Non-CT (N=21,680)	CT (N=21,680)	
T stage			0.658
T1	963 (4.4)	936 (4.3)	
T2	1,857 (8.6)	1,866 (8.6)	
T3	14,845 (68.5)	14,772 (68.1)	
T4	4,015 (18.5)	4,106 (18.9)	
N stage			0.163
N1	14,710 (67.9)	14,574 (67.2)	
N2	6,970 (32.1)	7,106 (32.8)	
Age (years)			1.000
≤65	6,261 (28.9)	6,261 (28.9)	
>65	15,419 (71.1)	15,419 (71.1)	
Race			0.053
White	17,248 (79.6)	17,384 (80.2)	
Black	2,629 (12.1)	2,629 (12.1)	
Other	1,803 (8.3)	1,667 (7.7)	
Gender			1.000
Male	10,775 (49.7)	10,775 (49.7)	
Female	10,905 (50.3)	10,905 (50.3)	
Tumor location			0.792
Cecum	5,722 (26.4)	5,858 (27.0)	
Ascending colon	4,624 (21.3)	4,624 (21.3)	
Hepatic flexure	1,078 (5.0)	1,078 (5.0)	
Transverse colon	2,066 (9.5)	2,066 (9.5)	
Splenic flexure	809 (3.7)	809 (3.7)	
Descending colon	1,295 (6.0)	1,295 (6.0)	
Sigmoid colon	6,086 (28.1)	5,950 (27.4)	
Grade			1.000
Grade I/II	15,717 (72.5)	15,717 (72.5)	
Grade III/IV	5,678 (26.2)	5,678 (26.2)	
Unknown	285 (1.3)	285 (1.3)	

NMA, non-mucinous adenocarcinoma; PSM, propensity score matching; CT, chemotherapy.

Table S3 Patient characteristics in stage III MAC after PSM

Characteristics	Number of patients (%)		P
	Non-CT (N=2,329)	CT (N=2,329)	
T stage			0.149
T1	41 (1.8)	50 (2.1)	
T2	155 (6.7)	191 (8.2)	
T3	1,543 (66.3)	1,497 (64.3)	
T4	590 (25.3)	591 (25.4)	
N stage			0.277
N1	1,463 (62.8)	1,427 (61.3)	
N2	866 (37.2)	902 (38.7)	
Age (years)			1.000
≤65	584 (25.1)	584 (25.1)	
>65	1,745 (74.9)	1,745 (74.9)	
Race			0.731
White	1,930 (82.9)	1,928 (82.8)	
Black	247 (10.6)	259 (11.1)	
Other	152 (6.5)	142 (6.1)	
Gender			0.860
Male	1,085 (46.6)	1,079 (46.3)	
Female	1,244 (53.4)	1,250 (53.7)	
Tumor location			0.164
Cecum	745 (32.0)	742 (31.9)	
Ascending colon	604 (25.9)	593 (25.5)	
Hepatic flexure	141 (6.1)	186 (8.0)	
Transverse colon	285 (12.2)	273 (11.7)	
Splenic flexure	103 (4.4)	92 (4.0)	
Descending colon	106 (4.6)	122 (5.2)	
Sigmoid colon	345 (14.8)	321 (13.8)	
Grade			0.163
Grade I/II	1,519 (65.2)	1,475 (63.3)	
Grade III/IV	681 (29.2)	738 (31.7)	
Unknown	129 (5.5)	116 (5.0)	

MAC, mucinous adenocarcinoma; PSM, propensity score matching; CT, chemotherapy.