IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2019; 10(2): 388-396. doi: 10.7150/jca.28014

Research Paper

Appraisal of Prognostic Interaction between Sidedness and Mucinous Histology in Colon Cancer: A Population-Based Study Using Inverse Probability Propensity Score Weighting

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Received: 2018.06.20; Accepted: 2018.10.03; Published: 2019.01.01

Abstract

Introduction: Colon cancer with different sidedness (right vs. left) and histology (mucinous vs. non-mucinous) may represent different disease entities. We investigated whether the prognostic values of sidedness and histology differed according to each other.

Materials and Methods: We analyzed 81342 patients with stage II–IV colon cancer from the Surveillance, Epidemiology, and End Results database between 2004 and 2012. Patients were divided into four subgroups on the basis of sidedness and histology: non-mucinous right-sided, non-mucinous left-sided, mucinous right-sided, and mucinous left-sided subgroups. Among each tumor stage, median overall survival (mOS) was compared between these subgroups after inverse probability propensity score weighting to handle confounding factors.

Results: In the stage IV subgroup, the prognosis for non-mucinous left-sided tumors (weighted mOS, 24.5 months) was significantly better than that for non-mucinous right-sided tumors (weighted mOS, 16.5 months; $P<0.001$) and that for mucinous left-sided tumors (weighted mOS, 16.5 months; $P<0.001$), whereas the survival was similar between left-sided and right-sided tumors with the mucinous subtype (weighted mOS, 16.5 months for both; $P=0.570$; test for interaction between sidedness and histology, $P_{interaction}<0.001$), and between mucinous and non-mucinous tumors in the right-sided colon (weighted mOS, 16.5 months for both; $P=0.207$). Similar findings were detected in the stage III subgroup ($P_{interaction}<0.001$). In the stage II subgroup, the survival was comparable among the four sidedness-histology subgroups ($P=0.159$ and $P_{interaction}=0.466$).

Conclusions: In stage III/IV colon cancer, the prognostic value of sidedness differed according to histology, and vice versa. By contrast, neither should be considered in risk stratification for stage II colon cancer.

Key words: colon cancer, tumor side, mucinous histology, survival, surveillance, epidemiology, end results

Introduction

Colorectal cancer is one of the most common malignancies and among the leading causes of cancer-related deaths worldwide. [1] Researchers have recently focused on analyzing the diversity of molecular profiles within the large intestine; [2] there is also renewed interest in clinicopathologic features as prognostic and predictive indicators, such as side

(i.e., right vs. left) of the primary tumor [3] and histologic type (i.e., mucinous vs. non-mucinous). [4]

Previous studies have shown that compared to patients with left-sided colon cancer (LSCC), those with right-sided colon cancer (RSCC) tend to be older and of the female gender, and have poorly differentiated and advanced stage tumors. [5-7] Additionally, RSCC exhibits a different molecular profile from LSCC. [8-10] However, data comparing prognosis between RSCC and LSCC are conflicting, particularly when patients are stratified by tumor stage. [3, 6, 7, 11, 12]

Mucinous adenocarcinoma (MAC) is a tumor comprising more than 50% extracellular mucin. [13] MAC is more often correlated with right sidedness, advanced stage at presentation, and peritoneal dissemination, and has different molecular biological patterns than non-mucinous adenocarcinoma (NMAC). [4, 14-16] However, the prognostic value of the mucinous histology remains controversial. Several studies reported that MAC was associated with poor prognosis, [16-18] while others did not confirm this conclusion. [4, 19-21]

To our knowledge, data are scarce regarding the prognostic impact of sidedness and histology stratified by each other. We suspect that non-mucinous RSCC, non-mucinous LSCC, mucinous RSCC, and mucinous LSCC might represent different disease entities. In the present population-based study of patients with stage II–IV colon cancer, we aim to investigate whether the prognostic impacts of tumor side and histology on patient survival differ according to each other.

Materials and Methods

Study cohort

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (18 registries), we identified 254040 patients with colon cancer diagnosed between January 2004 and December 2012. As presented in **Figure 1**, 81342 patients met the inclusion criteria for this study. Because SEER is public-use data, no institutional review was sought and informed consent was waived.

Overall survival (OS) was the primary outcome of interest. The examined covariates included race, age, sex, marital status, year of diagnosis, SEER region, tumor grade, tumor location, tumor histologic type, T and N category (6th edition), and the total number of lymph nodes evaluated.

Patients with cancer of the cecum, ascending colon, and transverse colon were defined as having RSCC, and patients with cancer of the descending or sigmoid colon were considered as having LSCC. NMAC was defined on the basis of the third edition of the International Classification of Diseases for Oncology histology codes 8140, 8144, 8210, 8211, 8221, 8261, 8262, and 8263 and MAC, on the basis of the codes 8480 and 8481. Patients were further divided into four subgroups on the basis of sidedness and histology (S-H): non-mucinous RSCC, non-mucinous LSCC, mucinous RSCC, and mucinous LSCC.

This study is based on SEER database which is public-use data, thus no institutional review was sought and informed consent was waived.

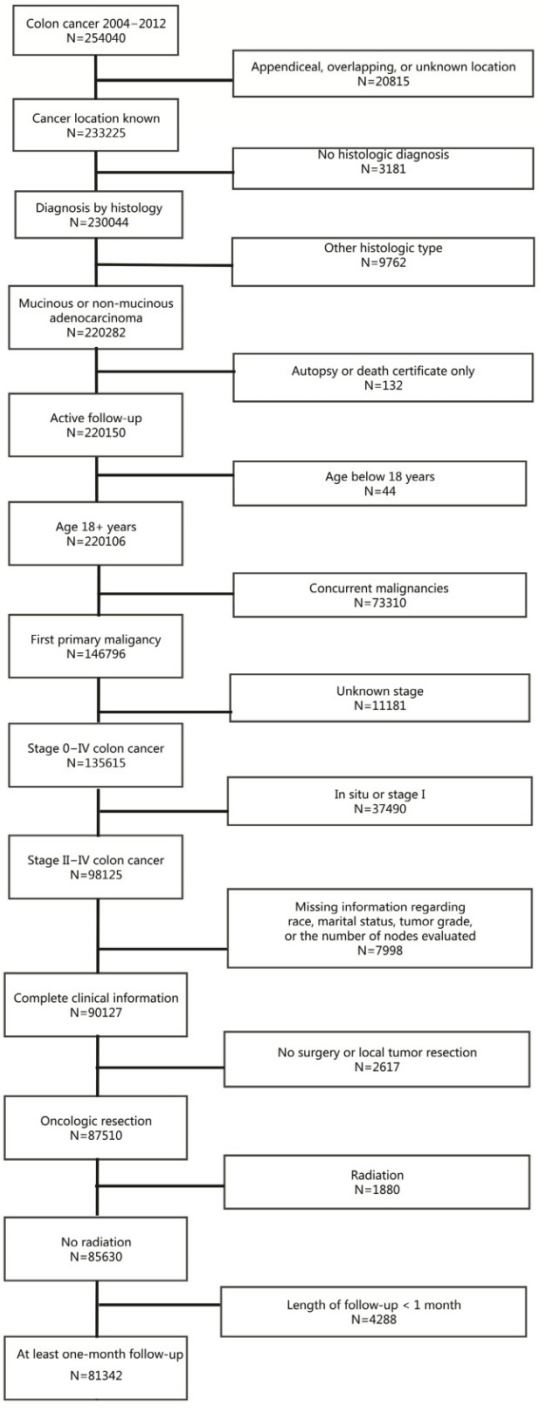

Figure 1. Flowchart of patient selection process for the study cohort.

Statistical analysis

The χ^2 test was used to compare baseline clinicopathologic features between the S-H groups. To allow for more accurate measurement of the prognostic impact of sidedness and histology, we used an inverse probability propensity score weighting approach for multiple groups (≥ 2) [22] with stratification for tumor stage to generate a weighted cohort in which the clinicopathologic features (i.e., age, sex, race, marital status, year of diagnosis, SEER region, tumor grade, T and N stage, and total evaluated lymph node count) were balanced between each pair of S-H groups. Propensity score methods are useful to reduce or minimize the effects of confounding when estimating the effects of treatments, exposures, or interventions in observational or non-randomized interventional studies. [23] It has been shown that that both the inverse propensity score weighting and propensity score matching allow for the estimation of the causal effect with minimal bias. [24] As compared with the propensity score matching approach, inverse propensity score weighting can be more flexibly applied to comparison between multiple groups and hence was used in the current study. [22, 25]

After inverse propensity score weighting, OS was compared between the RSCC and LSCC groups and between the MAC and NMAC groups, as well as among the S-H groups. Survival curves for patients in different groups were generated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models with inverse propensity score weighting and robust sandwich variance estimators [26] were used to assess the associations of sidedness, histology, and S-H group with hazard ratios (HRs) for death. Interaction tests were performed to determine whether the impacts of sidedness and histology on OS were significantly influenced by each other using Cox proportional hazards models.

Statistical significance was set as $P < 0.050$ in a two-tailed test. Statistical analyses were performed using SAS v. 9.3 (SAS Institute, Cary, NC, USA), IBM SPSS Statistics for Windows v. 19.0 (IBM Corp., Armonk, NY, USA), and R v. 3.4.1 (http://www.r-project.org).

Results

Patient characteristics

Table 1 summarizes the patient characteristics of the study cohort (81342 cases). Overall, 49,398 (60.7%) patients had RSCC and 31,944 (39.3%) patients had LSCC, 9265 (11.4%) patients with MAC while 72077 (88.6%) patients with NMAC. The non-mucinous RSCC, non-mucinous LSCC, mucinous RSCC, and mucinous LSCC subgroups included 42395 (52.1%), 29682 (36.5%), 7003 (8.6%), and 2262 (2.8%) patients, respectively. The mean follow-up duration was 35.7 ± 29.3 months.

Table 1. Clinicopathologic characteristics of the study cohort of patients with stage II–IV colon cancer (N = 81342)

Variable	Number (%)
Tumor side	
Right	49398 (60.7%)
Left	31944 (39.3%)
Mucinous histology	
Yes	9265 (11.4%)
No	72077 (88.6%)
S-H group	
Non-mucinous RSCC	42395 (52.1%)
Non-mucinous LSCC	29682 (36.5%)
Mucinous RSCC	7003 (8.6%)
Mucinous LSCC	2262 (2.8%)
Age, years	
< 50	9153 (11.3%)
50–59	15133 (18.6%)
60–69	19170 (23.6%)
70–79	20017 (24.6%)
≥ 80	17869 (22.0%)
Sex	
Male	38748 (47.6%)
Female	42594 (52.4%)
Race	
Non-Hispanic white	56190 (69.1%)
Non-Hispanic black	10079 (12.4%)
Hispanic	8047 (9.9%)
Other	7026 (8.6%)
Marital status	
Married	45364 (55.8%)
Single/other	20034 (24.6%)
Widowed	15944 (19.6%)
Year of diagnosis	
2004–2006	27968 (34.4%)
2007–2009	27785 (34.2%)
2010–2012	25589 (31.5%)
SEER region	
Midwest	13160 (16.2%)
Northeast	12780 (15.7%)
South	15823 (19.5%)
West	39579 (48.7%)
Tumor grade	
G1/G2	62334 (76.6%)
G3/G4	19008 (23.4%)
T stage	
T1	1521 (1.9%)
T2	3226 (4.0%)
T3	60978 (75.0%)
T4	15617 (19.2%)
N stage	
N0	36044 (44.3%)
N1	26624 (32.7%)
N2	18674 (23.0%)
AJCC stage	
II	33414 (41.1)
III	32480 (39.9)
IV	15448 (19.0)
Total evaluated node count	
< 12	19635 (24.1%)
≥ 12	61707 (75.9%)

RSCC, right-sided colon cancer; LSCC, left-sided colon cancer; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer

Table 2. Patient characteristics of the study cohort stratified by tumor side and histology

Variable	RSCC (%)	LSCC (%)	*P* value	NMAC (%)	MAC (%)	*P* value
Mucinous histology			< 0.001			-
Yes	14.2	7.1		-	-	
No	85.8	92.9		-	-	
Age, years			< 0.001			< 0.001
< 50	8.6	15.3		11.6	11.2	
50–59	15.6	23.3		16.3	18.9	
60–69	22.9	24.7		22.3	23.7	
70–79	26.7	21.4		25.4	24.5	
≥ 80	26.3	15.3		24.3	21.7	
Sex			< 0.001			0.012
Male	44.7	52.2		46.4	47.8	
Female	55.3	47.8		53.6	52.2	
Race			< 0.001			< 0.001
Non-Hispanic white	71.2	65.7		71.9	68.7	
Non-Hispanic black	12.6	12.0		11.6	12.5	
Hispanic	9.3	10.9		10.1	9.9	
Other	6.9	11.4		6.3	8.9	
Marital status			< 0.001			< 0.001
Married	54.2	58.2		54.3	56.0	
Widowed	22.5	15.1		21.7	19.3	
Single/other	23.3	26.7		24.0	24.7	
Year of diagnosis			0.154			< 0.001
2004–2006	34.2	34.7		39.4	33.7	
2007–2009	34.1	34.2		31.9	34.4	
2010–2012	31.7	31.1		28.7	31.8	
SEER region			< 0.001			< 0.001
Midwest	17.0	14.9		17.3	16.0	
Northeast	16.0	15.2		18.4	15.4	
South	18.8	20.5		17.1	19.8	
West	48.2	49.3		47.2	48.8	
Tumor grade			< 0.001			< 0.001
G1/G2	72.6	82.9		74.9	76.9	
G3/G4	27.4	17.1		25.1	23.1	
T stage			< 0.001			< 0.001
T1	1.3	2.7		0.8	2.0	
T2	3.6	4.5		2.9	4.1	
T3	75.6	74.0		71.1	75.5	
T4	19.4	18.9		25.2	18.4	
N stage			< 0.001			< 0.001
N0	45.9	41.9		46.7	44.0	
N1	30.8	35.7		28.7	33.2	
N2	23.3	22.4		24.6	22.7	
AJCC stage			< 0.001			< 0.001
II	43.3	37.3		43.8	40.7	
III	38.8	41.6		37.5	40.2	
IV	17.9	20.7		18.8	19.0	
Total evaluated node count			< 0.001			0.002
< 12	20.0	30.5		22.9	24.3	
≥ 12	80.0	69.5		77.1	75.7	

RSCC, right-sided colon cancer; LSCC, left-sided colon cancer; MAC, mucinous adenocarcinoma; NMAC, non-mucinous adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer

As shown in **Table 2**, MAC was more often present on the right side of the colon (14.2% vs. 7.1%, $P < 0.001$). Because of the large sample size, statistically significant imbalances were detected in all patient characteristics between the RSCC and LSCC groups (except year of diagnosis) and between the MAC and NMAC groups. However, absolute differences in the proportions were numerically small. Of note, compared to patients with LSCC, those with RSCC were markedly more likely to be female (55.3% vs. 47.8%), non-Hispanic white (71.2% vs. 65.7%), and older than 80 years of age (26.3% vs. 15.3%), and they had poorly or non-differentiated (27.4% vs. 17.1%) tumors, stage II tumors (43.3% vs. 37.3%), and ≥ 12 evaluated nodes (80.0% vs. 69.5%). More patients with MAC had T4 disease (25.2% vs. 18.4%) compared to patients with NMAC.

After inverse propensity score weighting, patient characteristics were well balanced between each pair of the four S-H groups in all three stage subgroups (**Supplementary Tables A-C**).

Prognostic impact of sidedness in stage II–IV subgroups

After inverse propensity score weighting, the median OS was significantly better in LSCC than in RSCC in the stage IV subgroup (20.5 vs. 16.5 months; HR for RSCC, 1.15 [95% CI, 1.11–1.19]; P < 0.001; **Figure 2A**). The weighted 3-year OS rates for RSCC and LSCC were numerically similar in the stage III (68.6% and 69.9%, respectively; **Figure 2B**) and stage II subgroups (81.3% and 80.5%, respectively; **Figure 2C**), although the differences were statistically significant due to the large sample size (stage III subgroup: HR for RSCC, 1.06 [95% CI, 1.01–1.09]; P = 0.006; stage II subgroup: HR for RSCC, 0.93; 95% CI, 089–0.97; P = 0.006).

Prognostic value of mucinous histology by stage

The weighted OS was significantly worse for MAC than NMAC in the stage IV (median OS, 16.9 vs. 19.5 months; HR for MAC, 1.15 [95% CI, 1.09−1.22]; $P < 0.001$; **Figure 3A**) and stage III subgroups (3-year OS, 67.0% vs. 71.5%; HR for MAC, 1.13 [95% CI, 1.07−1.19]; $P < 0.001$; **Figure 3B**). In the stage II subgroup, the weighted 3-year OS rates were similar for MAC and NMAC (81.0% and 80.8%, respectively; HR for MAC, 1.01 [95% CI, 0.88−1.16]; $P = 0.853$; **Figure 3C**).

In the stage III subgroup with inverse propensity score weighting, the prognostic interaction between sidedness and histology was also statistically significant ($P_{interaction} < 0.001$; **Figure 4B** and **Table 3**). The prognosis for non-mucinous RSCC was worse than for non-mucinous LSCC (3-year OS: 69.0% vs. 73.9%; HR, 1.14 [95% CI, 1.10–1.19]; P < 0.001), whereas the prognosis for mucinous RSCC was similar to that for mucinous LSCC (3-year OS: 68.2% vs. 65.6%; HR, 0.96 [95% CI, 0.85–1.09]; P = 0.531). The prognosis for MAC on the left-hand side was markedly worse than NMAC on this side (3-year OS: 65.6% vs. 73.9%; HR, 1.23 [95% CI, 1.11–1.38]; P < 0.001), whereas the survival rates for MAC and NMAC on the right-hand side were similar (3-year OS: 68.2% vs. 69.0%; HR, 1.04 [95% CI, 0.97–1.11]; P = 0.300).

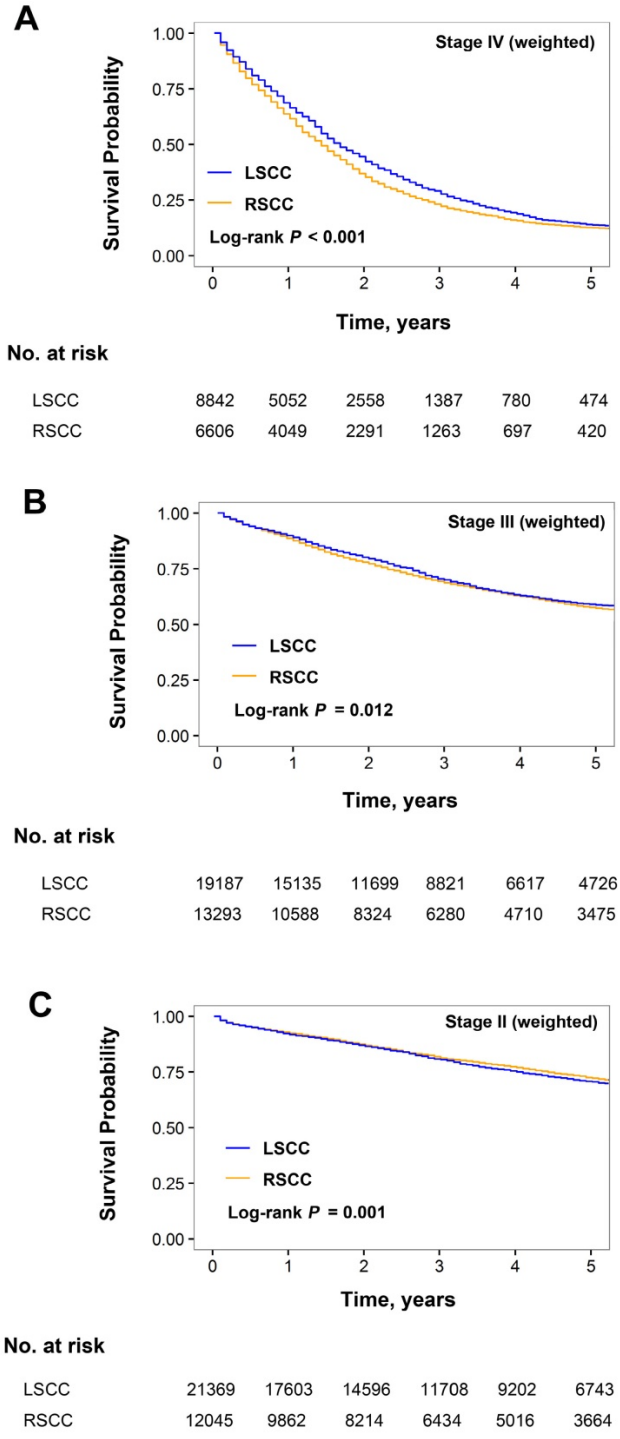

Figure 2. Kaplan–Meier estimates of overall survival of patients with right-sided colon cancer (RSCC) and left-sided colon cancer (LSCC). (A) Stage IV, (B) III, and (C) II subgroups weighted by inverse propensity score.

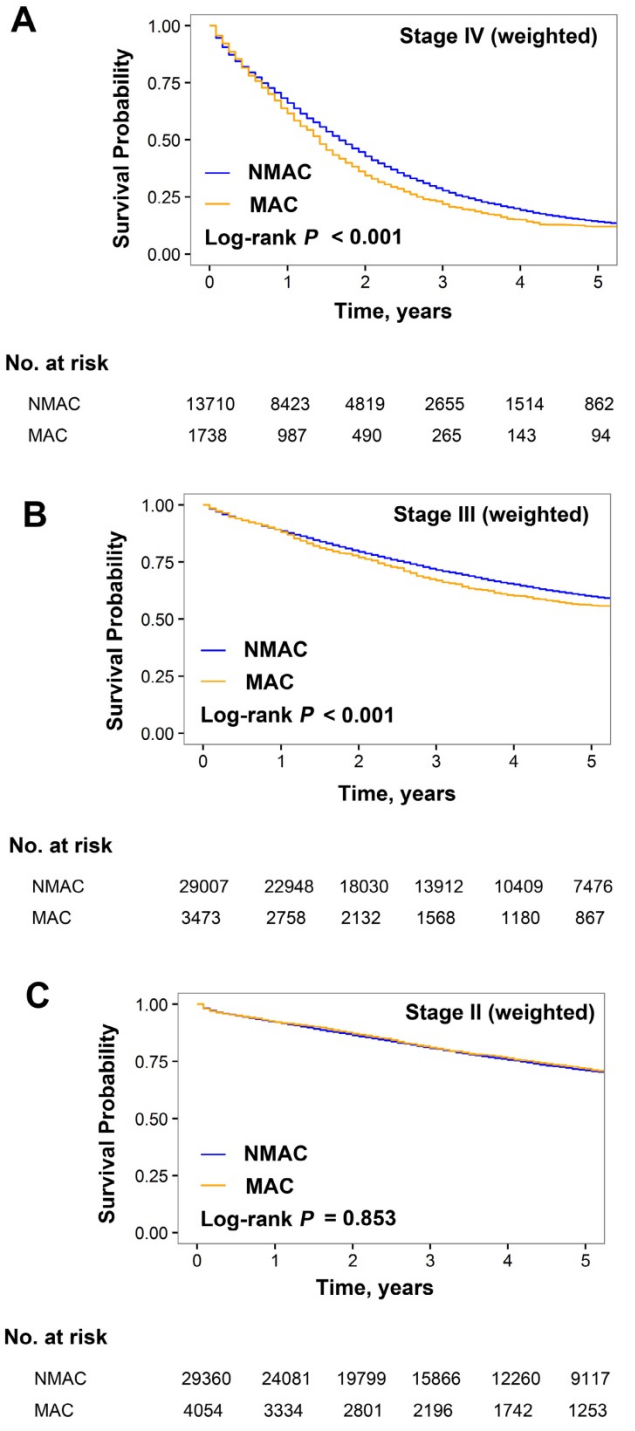

Figure 3. Kaplan–Meier estimates of overall survival for patients with mucinous adenocarcinoma (MC) and non-mucinous adenocarcinoma (NMC). (A) Stage IV, (B) III, and (C) II subgroups weighted by inverse propensity score.

In the stage II subgroup, the weighted 3-year OS rates were similar between the non-mucinous RSCC, non-mucinous LSCC, mucinous RSCC, and mucinous LSCC groups (81.0%, 80.6%, 81.6%, and 80.5%, respectively; P = 0.159; **Figure 4C** and **Table 3**). Additionally, the interaction between tumor side and histology was insignificant ($P_{interaction}$ = 0.466).

Prognostic interaction between tumor side and histology

In the stage IV subgroup weighted by inverse propensity score, the impact of sidedness on survival significantly differed according to tumor histology, and vice versa (test for interaction between sidedness and histology, $P_{interaction}$ < 0.001; **Figure 4A** and **Table 3**). Patients with non-mucinous RSCC showed an

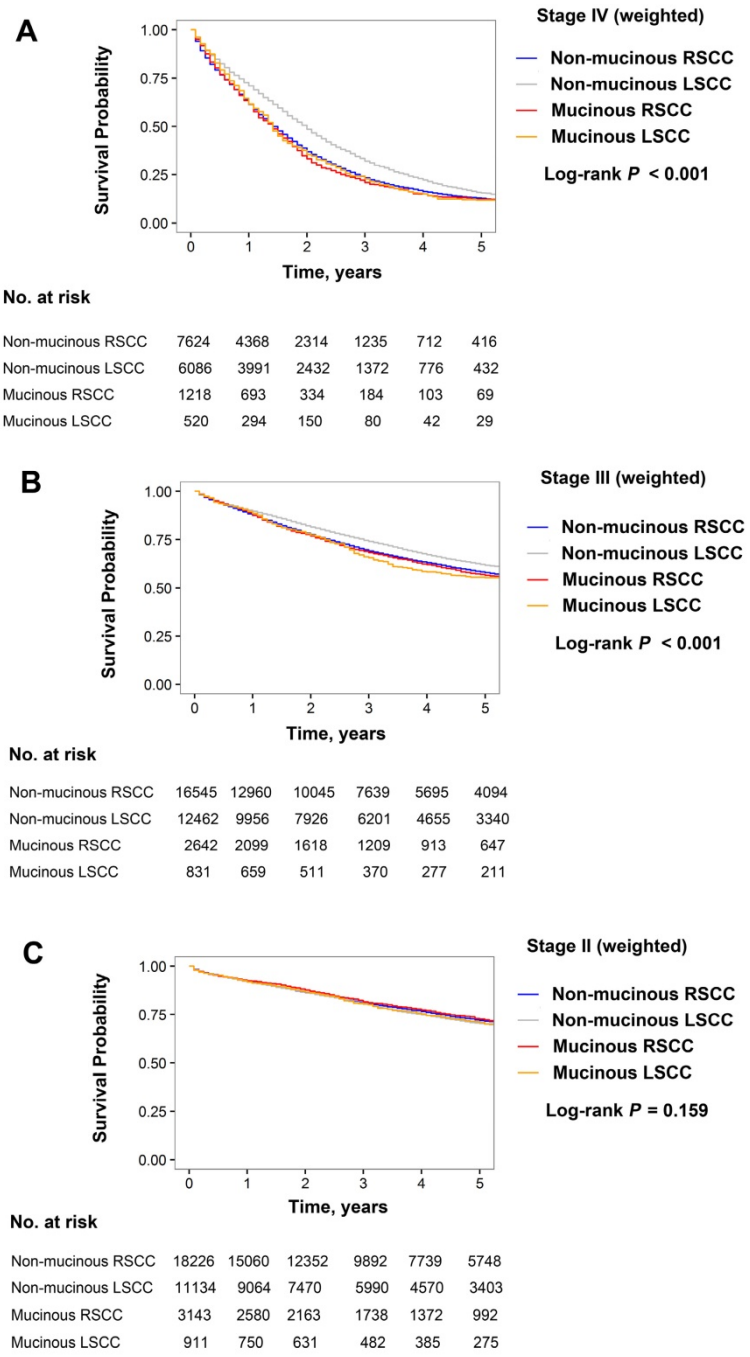

Figure 4. Kaplan–Meier estimates of overall survival for patients with non-mucinous right-sided colon cancer (RSCC), non-mucinous left-sided colon cancer (LSCC), mucinous RSCC, and mucinous LSCC. (A) Stage IV, (B) III, and (C) II subgroups weighted by inverse propensity score.

8-month decrease in median OS compared to those with non-mucinous LSCC (16.5 vs. 24.5 months; HR, 1.26 [95% CI, 1.21–1.31]; P < 0.001), whereas patient survival was similar for mucinous RSCC and mucinous LSCC (median OS: 16.5 months for both; HR for mucinous RSCC, 1.03 [95% CI, 0.92–1.16]; P = 0.570). Additionally, mucinous LSCC demonstrated an 8-month decrease in median OS compared with non-mucinous LSCC (16.5 vs. 24.5 months; HR, 1.27 [95% CI, 1.14–1.41]; P < 0.001), whereas patient survival was similar for mucinous RSCC and non-mucinous RSCC (median OS: 16.5 months for both; HR for mucinous RSCC, 1.05 [95% CI, 0.97–1.12]; P = 0.207).

Sensitivity analysis

For sensitivity analysis, we repeated the primary analyses after excluding patients with transverse colon cancer (10536 cases) or re-classifying these patients into the LSCC group. Additionally, we repeated the analyses after excluding patients in the tails of the distribution of propensity scores. [27]

Under these circumstances, the conclusions were consistent with those of the primary analyses (data not shown).

Table 3. Kaplan-Meier estimates of overall survival (OS) and hazard ratios weighted by inverse propensity score

Variable	*N*	3-y OS (%)	Median OS (months)	Hazard ratio (95% CI)	*P* value
Stage IV subgroup	15448				
Tumor side					
Non-mucinous LSCC	6086	32.1	24.5	1	
Non-mucinous RSCC	7624	23.3	16.5	1.26 (1.21−1.31)	< 0.001
Mucinous LSCC	520	22.8	16.5	1	
Mucinous RSCC	1218	20.8	16.5	1.03 (0.92−1.16)	0.570
Mucinous histology					
Non-mucinous LSCC	6086	32.1	24.5	1	
Mucinous LSCC	520	22.8	16.5	1.27 (1.14−1.41)	< 0.001
Non-mucinous RSCC	7624	23.3	16.5	1	
Mucinous RSCC	1218	20.8	16.5	1.05 (0.97−1.12)	0.207
Stage III subgroup	32480				
Tumor side					0.012
Non-mucinous LSCC	12462	73.9	99.5	1	
Non-mucinous RSCC	16545	69.0	87.5	1.14 (1.10−1.19)	< 0.001
Mucinous LSCC	831	65.6	79.5	1	
Mucinous RSCC	2642	68.2	83.0	0.96 (0.85−1.09)	0.531
Mucinous histology					
Non-mucinous LSCC	12462	73.9	99.5	1	
Mucinous LSCC	831	65.6	79.5	1.23 (1.11−1.38)	< 0.001
Non-mucinous RSCC	2642	69.0	87.5	1	
Mucinous RSCC	16545	68.2	83.0	1.04 (0.97−1.11)	0.300
Stage II subgroup					
Tumor side					
Non-mucinous LSCC	11134	80.6	Not reached	1	
Non-mucinous RSCC	18226	81.0	Not reached	0.96 (0.91−1.00)	0.072
Mucinous LSCC	911	80.5	Not reached	1	
Mucinous RSCC	3143	81.6	Not reached	0.90 (0.78−1.05)	0.176
Mucinous histology					
Non-mucinous LSCC	11134	80.6	Not reached	1	
Mucinous LSCC	911	80.5	Not reached	1.04 (0.91−1.19)	0.540
Non-mucinous RSCC	18226	81.0	Not reached	1	
Mucinous RSCC	3143	81.6	Not reached	0.98 (0.91−1.06)	0.692

RSCC, right-sided colon cancer; LSCC, left-sided colon cancer.

Discussion

To the best of our knowledge, this is the first study that demonstrates that the prognostic impacts of tumor side and mucinous histology are affected by each other in stage III−IV colon cancer; that is, the prognosis for non-mucinous LSCC was significantly better than that for non-mucinous RSCC and that for mucinous LSCC, whereas the survival was similar between left-sided and right-sided MAC, and between mucinous and non-mucinous RSCC. In contrast, the survival was comparable among the four S-H subgroups for stage II colon cancer.

A number of previous studies have investigated the impact of sidedness and histology on survival outcomes for patients with colon cancer, reaching inconsistent conclusions. [3, 4, 6, 7, 11, 12, 19-21] None of these studies has taken into account sidedness, histology, and tumor stage simultaneously; to our knowledge, this is the first study to perform elaborate survival analyses with stratification for sidedness, histology, and tumor stage. The non-straightforward prognostic impact of sidedness and histology across different tumor stages, as well as the prognostic interaction between sidedness and histology for stage III/IV tumors, might partially explain the conflicting data in the previous studies.

Since clinicopathologic factors are optimally balanced by inverse propensity score weighting, tumor biology most probably drives the complex association of sidedness and histology with survival. Not only unfavorable molecular features (e.g., BRAF mutation, KRAS mutation, and CpG island methylation) but also favorable ones (e.g., deficient DNA mismatch repair [dMMR], chromosome stability and diploid) are more common in RSCC and MAC. [8, 9, 16, 28-32] As shown previously, the overall percentage of dMMR was up to 22% in stage II colon cancer, [33] which could partially balance out the negative prognostic impact of right sidedness and mucinous histology in the stage II subgroup. Moreover, the efficacy of chemotherapy and biologic agents may differ according to tumor side and histology, particularly in stage IV colon cancer. In the *post hoc* analysis of the FIRE1 trial, LSCC showed greater benefit from first-line cytotoxic chemotherapy than RSCC. [34] Additionally, reports of subgroup analysis from the FIRE3 and CALGB/SWOG 80405 trials suggest that patients with RSCC benefit less from anti-EGFR therapy than those with LSCC. [3, 35] Moreover, it was reported that MAC showed a poorer response to cytotoxic chemotherapeutic regimens than NMAC. [15, 16, 36] In the present study, the presence of either right sidedness or mucinous histology was correlated with an 8-month decrease in median OS and an over 25% increase in risk of death as compared with non-mucinous left-sided tumors in the stage IV subgroup, and the prognoses were similarly poor for stage IV non-mucinous RSCC, mucinous RSCC, and mucinous LSCC (16.5 months for all). Taken together, these findings suggest that both sidedness and histology should be considered during clinical decision-making processes and adopted as risk-stratification factors for advanced colon cancer. Moreover, recent studies suggest that despite dismal prognosis, the Commonsense Molecular Subtype 1 (predominantly right-sided tumors) and MAC are more likely to have a higher mutation count and stronger immune infiltration and activation.[2, 37] Therefore, further researches are warranted to investigate whether right-sidedness and/or mucinous histology can be used as additional markers to dMMR or high microsatellite instability for selecting candidates for PD-1 blockade. [38, 39]

The therapeutic value of adjuvant chemotherapy in stage II colon cancer remains controversial, highlighting the need for effective risk-stratifying factors. Previous studies showed that the efficacy of adjuvant chemotherapy did not differ between stage II RSCC and LSCC or between stage II MAC and NMAC. [17, 19] Because of lack of evidence, current guidelines do not include right-sidedness and mucinous histology in the risk factor list for decision-making regarding adjuvant chemotherapy. [40] In the current study, the survival was similar in the four S-H groups for stage II colon cancer, which supports the current recommendation that consider neither of these factors when evaluating the administration of adjuvant treatment for stage II colon cancer.

The present study has some limitations. First, only limited data on patient-level characteristics have been provided by the SEER database, whereas data on patient comorbidities and performance status, tumor molecular features, and chemotherapy and chemotherapeutic regimens are unavailable. Because we assessed OS as the endpoint, medical comorbidities or other competing causes of death might influence our results. Still, OS is the most valuable endpoint for cancer patients and has no difference in definition between hospitals. Moreover, although the definition of the mucinous histology has been standardized, there might be variations in the diagnosis depending on the interpretation of the individual pathologist, which might result in misclassification. Despite these limitations, given the large sample size and the population-based nature of the SEER database, we are able to perform adequately powered survival analyses stratified by tumor side, histology, and stage, which is hard to achieve with single-institution studies.

Conclusion

In conclusion, the prognostic values of right sidedness and mucinous histology were mutually influenced for stage III and IV colon cancer. In contrast, the impacts of sidedness and histology on survival were minimal and independent of each other for stage II colon cancer. Thus, we recommend including both sidedness and histology as risk-stratification factors for patients with stage III/IV colon cancer but neither for those with stage II colon cancer.

Acknowledgements

We feel grateful that this work was supported by the Natural Science Foundation of Guangdong Province [grant number 2014A030312015]; Science and Technology Program of Guangdong [grant number 2015B020232008]; Science and Technology Program of Guangzhou [grant number 15570006, 201508020250, 201604020003]. We also thank the staff members of the National Cancer Institute and their colleagues across the United States and at Information Management Services, Inc., who have been involved with the Surveillance, Epidemiology, and End Results (SEER) Program.

Competing Interests

The authors have declared that no competing interest exists.

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