Original Article

Prognosis and efficiency of adjuvant therapy in resected colon signet-ring cell carcinoma

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Background: Colon signet-ring cell carcinoma (SRCC) is associated with poor survival compared with other histologic subtypes such as adenocarcinoma (AC) and mucinous adenocarcinoma (MC). This present study analyzed the prognosis factors of SRCC and assessed whether the adjuvant therapy could supply benefit for SRCC with different regimens.

Methods: Data on 82,606 colon cancer patients who received surgery in the period 1992–2005 was included in this population-based study. The survival benefit was evaluated using a Cox proportional hazards model and propensity score (PS)-matched techniques.

Results: SRCC was found in 779 (0.9%) patients who were more frequently in stage III and IV colon cancer than other subtypes. The 5-year survival of SRCC patients were 30.1% (95% CI, 26.7–33.5%) which was significantly lower compared with 51.6% (95% CI, 51.3–52.0%) for AC and 48.8% (95% CI, 47.8–49.8%) for MC. For patients in stage II, there was no significantly difference between chemo group and no-chemo group in all histologic subtypes. The results in stage III showed that 5-FU based adjuvant chemotherapy for AC and SRCC patients could improve overall survival (OS) which could be further enhanced by adding oxaliplatin. The similar benefit was found in stage IV patients. However, there was no significantly difference between different therapy regimens in stage IV SRCC patients.

Conclusions: Although the prognosis of patients with colon SRCC was pessimistic, the effective role of adjuvant therapy for OS was still observed in stage III SRCC patients who received surgery. Similarly, patients with stage IV SRCC could also gain benefit from systemic therapy.

Keywords: Colon cancer; Surveillance, Epidemiology, and End Results (SEER) program; signet-ring cell carcinoma (SRCC); adjuvant therapy; prognosis

Submitted Mar 16, 2018. Accepted for publication Jul 12, 2018.
doi: 10.21037/tcr.2018.07.14
View this article at: http://dx.doi.org/10.21037/tcr.2018.07.14

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer related death in the United States (1,2). Three major histological subtypes of CRC have been defined by the World Health Organization including adenocarcinoma (AC), mucinous adenocarcinoma (MC) and signet-ring cell adenocarcinoma (SRCC) (3). ACs are the most common subtype of CRC, with MCs accounting for approximately 10% of cases, and SRCCs accounting for only one percent of cases (4,5). The SRCC subtype was first described in 1951 by Laufman and Saphir as an intracellular

mucous accumulation and indenting of the nuclei to margin (6). SRCC is characteristically associated with younger patients, lower curative resection rates, localization to the right hemi colon, having an advanced tumor-node-metastasis (TNM) stage and higher peritoneal metastasis (5,7-9). The mechanism of its malignant biological behavior may be due to its higher invasive potential, which may be influenced by higher expression of proteolytic enzymes and lower expression of adhesion molecules than other subtypes of CRC (10,11). At present, investigations have indicated that SRCC has a poorer prognosis and is less responsive to treatment than other subtypes of CRC. The 5-year survival rate of SRCC patients has been found to be less than 30% with a median survival time of 1 to 3 years (12-14). However, whether the prognostic impact is relevant for colon cancer patients is still poorly understood.

Treatments for colon cancer have improved in recent years, providing more effective treatment strategies. The use of adjuvant therapy remains a controversial option for the treatment of stage II colon cancer patients (15,16). However, adjuvant chemotherapy with fluorouracil has been shown to improve the prognosis of stage III colon cancer patients following tumor resection (17). While oxaliplatin has become a standard component of treatments such as FOLFOX or CapeOx, there are still some studies which suggest that oxaliplatin may not be applicable for all patients receiving chemotherapy (18,19). It is unclear whether distinguishing between CRC histological subtypes could aid in the selection of an appropriate chemotherapeutic strategy. The CRC histological subtypes are neither mentioned as factors for selection of colon cancer adjuvant chemotherapy in National Comprehensive Cancer Network (NCCN) or the European Society for Medical Oncology (ESMO). Moreover, there are few studies which focus on the influence of distinct histological subtypes on how CRC patients respond to treatment. Hugen *et al*. found that adjuvant chemotherapy could improve the survival of stage III colon SRCC patients with data from the Netherlands Cancer Registry (14). However, additional studies focusing on different stages and treatment strategies of colon SRCC are needed to inform the clinical practice.

In this population-based retrospective study, we analyze the clinicopathological characteristics of different histological subtypes of colon cancer. We then establish the prognostic impact of colon SRCC, assessing the relative benefits of distinct chemotherapeutic regimens on colon SRCC patients following resection.

Methods

Data source

The present study was a retrospective analysis using data acquired from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. This study was conducted in accordance with a SEER-Medicare data use agreement. A study protocol approval was also granted by the First Hospital of China Medical University Institutional Review Board.

SEER data contains information on patient demographics, tumor and disease characteristics, course of treatment, use of cancer-directed operative and medical therapy, survival, and cause of death for individuals diagnosed with cancer. It is a population-based cancer registry covering approximately 28% of the US population across several disparate geographic regions (20). Medicare is the primary health insurer for approximately 97% of the US population aged ≥65 years (21). The unmentioned details of the database were described elsewhere (22).

Patient selection

All Medicare-registered patients diagnosed with incident malignant primary colon cancer (SEER cancer site codes: 18.0, 18.2–18.9) between 1992 and 2009 in a SEER area were considered for study inclusion. The study contained three histological types defined by WHO International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), codes: AC [8010, 8020–8022, 8140–8141, 8144–8145, 8210–8211, 8220–8221, 8230–8231, 8260–8263], MC [8480] and SRCC [8490].

For stage II–III colon cancer, patients who underwent primary tumor resection with likely curative intent within 180 days of diagnosis. The no-chemo group was designated as patients with no claim of postoperative chemotherapy within 9 months after operation. The 5-FU group consisted of patients who only received 5-FU/capecitabine chemotherapy within 9 months of surgery. The FOLFOX group comprised patients with any record of oxaliplatin plus 5-FU/capecitabine within 9 months of surgery.

For stage IV colon cancer, patients were selected who received surgery within 180 days of diagnosis. The no-chemo group was designated as no claim of perioperative chemotherapy from the day of diagnosis to 9 months after operation. The 5-FU group consisted of patients who only received 5-FU/capecitabine chemotherapy

from the diagnosis day to 9 months after surgery. The FOLFOX/FOLFIRI group comprised patients with any record of oxaliplatin or irinotecan plus 5-FU/capecitabine from the day of diagnosis to 9 months after surgery. The Bevacizumab group selected patients who received FOLFOX or FOLFIRI with bevacizumab from the diagnosis day to 9 months after operation.

Patients were eliminated from the study population if they: (I) were stage II–III patients who received any preoperative neoadjuvant treatment; (II) received postoperative radiotherapy; (III) had prior non-colon cancer; (IV) had incomplete histological subtype or pathological stage entries; (V) died within 30 days after tumor resection.

Variables

Subjects were categorized by age at diagnosis, year of diagnosis, gender, race, marital status, residence (rural or urban), median household income, level of education (percentage of people aged >25 years with <12 years of education). To control for the effects of comorbidities, analyses were adjusted by the Centers for Medicare and Medicaid Services Hierarchical Condition Category (HCC) based on Medicare outpatient and inpatient claims for miscellaneous comorbidities within the 12 months before colon cancer diagnosis. The HCC risk score summarizes the health care problems and forecasts the future health care cost of a population compared with the average Medicare beneficiary (23).

The postoperative pathological stage was designated via the seventh edition of the Union for International Cancer Control (UICC) TNM staging system (24). Other covariates included histological grade, histological subtype, intestinal obstruction, intestinal perforation, and the number of lymph nodes examined.

Statistical analysis

The χ^2 test was used to compare demographics and tumor characteristics between the different groups. In the univariate survival analysis, overall survival (OS) was analyzed by the Kaplan-Meier method. Comparison of survival curves was carried out using the log-rank test. Because treatment choice estimates are likely confounded by factors related to treatment selection, a propensity score (PS)-matched analysis was performed to compare the effect of treatment on survival among patients of similar risk profiles as assessed by measured known confounders (25,26). PS matching is a statistical procedure for reducing this bias by assembling a sample in which confounding factors are balanced between treatment groups. Univariate logistic regression was used to find factors related to treatment selection (P<0.05). Multivariate logistic regression was used to estimate the PSs in each group. The PS-matched sample would then be constructed using "psmatch2" software package in STATA 12.0. A Cox proportional hazards model was also used in the adjusted analysis. The covariates included all variables that were identified to be significantly related to survival in the univariate analysis. All statistical analyses and graphics were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), STATA 12.0 software (STATA, College Station, TX, USA), and PASW Statistics 18.0 software (SPSS, Inc., Somers, NY, USA). For all analyses, a P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 82,606 patients were included in the present study, with most cases diagnosed as ACs (n=71,656, 86.7%). MCs were found in 12.3% patients and SRCCs accounted for just 0.9% of colon cancer patients who had received surgery (*Table 1*). In SRCC patients, the primary tumors were more frequently found in the right-side colon (83.1%) than AC (63.1%) or MC (78.3%) patients (P<0.01). SRCC patients also presented more frequently with a poor and undifferentiated histologic grade than the AC or MC groups (82.7% *vs.* 21.4%, 21.5%, P<0.01, respectively). Regarding the pTNM stages, SRCC patients were more likely to be diagnosed as pT4 (25.8%) compared with AC patients (11.7%) or MC patients (15.3%). SRCC patients were also more likely to be diagnosed as pN3 (42.1% *vs.* 13.8%, 17.1%, P<0.01, respectively). Furthermore, more stage III and IV patients were observed to have the SRCC subtype than AC or MC subtype (stage III 47.5% *vs.* 27.4%, 30.4%, P<0.01; stage IV 24.9% *vs.* 14.1%, 15.5%, P<0.01, respectively). Compared with the AC (33.6%) and MC (34.1%) groups, patients in the SRCC group (42.5%) were found to be more likely to suffer from intestinal obstruction after surgery (P<0.01).

Subtype as a prognostic factor

Patients in the SRCC group had a statistically significant poorer 5-year survival than patients in the AC or MC groups

Table 1 Demographic and clinicopathological features of patients with colon cancer diagnosed between 1992 and 2009

Features	AC (%), n=71,656	MC (%), n=10,175	SRCC (%), n=775	P
Gender				<0.01
Male	30,519 (42.6)	3,781 (37.2)	312 (40.3)	
Female	41,137 (57.4)	6,394 (62.8)	463 (59.7)	
Age at diagnosis, years				<0.01
<70	9,572 (13.4)	1,204 (11.8)	96 (12.4)	
70–74	15,676 (21.9)	2,131 (20.9)	177 (22.8)	
75–79	17,240 (24.1)	2,381 (23.4)	178 (23.0)	
80–85	17,552 (24.5)	2,575 (25.3)	193 (24.9)	
>85	11,616 (16.2)	1,884 (18.5)	131 (16.9)	
Race				<0.01
White	60,916 (85.0)	8,900 (87.5)	688 (88.8)	
Black	6,063 (8.5)	758 (7.4)	47 (6.1)	
Asian	2,141 (3.0)	212 (2.1)	20 (2.6)	
Other	2,536 (3.5)	305 (3.0)	20 (2.6)	
Marital status				<0.01
Single + separated	5,838 (8.1)	830 (8.2)	60 (7.7)	
Married	35,530 (49.6)	4,793 (47.1)	367 (47.4)	
Divorced + widowed	27,881 (38.9)	4,222 (41.5)	322 (41.5)	
Other	2,407 (3.4)	330 (3.2)	26 (3.4)	
Residence location*				0.087
Big metro	38,157 (53.3)	5,535 (54.4)	421 (54.3)	
Metro or urban	25,248 (35.2)	3,443 (33.8)	270 (34.8)	
Less urban or rural	8,248 (11.5)	1,197 (11.8)	84 (10.8)	
Median household income				0.041
1st quartile	17,795 (24.8)	2,642 (26.0)	186 (24.0)	
2nd quartile	18,060 (25.2)	2,432 (23.9)	181 (23.4)	
3rd quartile	17,902 (25.0)	2,533 (24.9)	204 (26.3)	
4th quartile	17,899 (25.0)	2,568 (25.2)	204 (26.3)	
Level of education				0.020
1st quartile	17,137 (23.9)	2,399 (23.6)	225 (29.0)	
2nd quartile	17,080 (23.8)	2,477 (24.3)	190 (24.5)	
3rd quartile	17,113 (23.9)	2,473 (24.3)	167 (21.5)	
4th quartile	17,243 (24.1)	2,380 (23.4)	159 (20.5)	
Unknown	3,083 (4.3)	446 (4.4)	34 (4.4)	
Year of diagnosis				<0.01
1992–1996	13,655 (19.1)	2,006 (19.7)	121 (15.6)	
1997–2000	12,866 (18.0)	1,993 (19.6)	148 (19.1)	
2001–2004	21,954 (30.6)	3,242 (31.9)	254 (32.8)	
2005–2009	23,181 (32.4)	2,934 (28.8)	252 (32.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Features	AC (%), n=71,656	MC (%), n=10,175	SRCC (%), n=775	P
Primary tumor site				<0.01
Left-sided colon	26,447 (36.9)	2,210 (21.7)	131 (16.9)	
Right-sided colon	45,209 (63.1)	7,965 (78.3)	644 (83.1)	
Histologic grade				<0.01
Well + moderate	53,949 (75.3)	7,226 (71.0)	54 (7.0)	
Poor + undifferentiated	15,343 (21.4)	2,186 (21.5)	641 (82.7)	
Unknown	2,364 (3.3)	763 (7.5)	80 (10.3)	
pT category				<0.01
pT1	8,333 (11.6)	406 (4.0)	18 (2.3)	
pT2	10,439 (14.6)	1,257 (12.4)	34 (4.4)	
pT3	38,255 (53.4)	5,950 (58.5)	413 (53.3)	
pT4a	4,886 (6.8)	894 (8.8)	106 (13.7)	
pT4b	3,489 (4.9)	662 (6.5)	94 (12.1)	
Unknown	6,254 (8.7)	1,006 (9.9)	110 (14.2)	
pN category				<0.01
pN0	45,254 (63.2)	5,999 (59.0)	258 (33.3)	
pN1	8,141 (11.4)	1,171 (11.5)	71 (9.2)	
pN2	8,343 (11.6)	1,268 (12.5)	119 (15.4)	
pN3a	5,605 (7.8)	881 (8.7)	98 (12.6)	
pN3b	4,313 (6.0)	856 (8.4)	229 (29.5)	
TNM stage				<0.01
I	16,394 (22.9)	1,394 (13.7)	34 (4.4)	
II	25,539 (35.6)	4,110 (40.4)	180 (23.2)	
III	19,646 (27.4)	3,093 (30.4)	368 (47.5)	
IV	10,077 (14.1)	1,578 (15.5)	193 (24.9)	
Intestinal obstruction				<0.01
No	47,585 (66.4)	6,703 (65.9)	446 (57.5)	
Yes	24,071 (33.6)	3,472 (34.1)	329 (42.5)	
Intestinal perforation				0.047
No	69,632 (97.2)	9,897 (97.3)	742 (95.7)	
Yes	2,024 (2.8)	278 (2.7)	33 (4.3)	
HCC risk score				<0.01
1st quartile	17,994 (25.1)	2,751 (27.0)	191 (24.6)	
2nd quartile	17,542 (24.5)	2,323 (22.8)	179 (23.1)	
3rd quartile	18,316 (25.6)	2,470 (24.3)	199 (25.7)	
4th quartile	17,804 (24.8)	2,631 (25.9)	206 (26.6)	
Number of examined lymph node				<0.01
<12	36,147 (50.4)	5,491 (54.0)	453 (58.5)	
≥12	35,509 (49.6)	4,684 (46.0)	322 (41.5)	

*, Variables have missing data. AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet-ring cell carcinoma.

following surgery (*Figure 1*). The SRCC 5-year survival rate was found to be 30.1% (95% CI, 26.7–33.5%), which is significantly lower than the 5-year survival rates of 51.6% (95% CI, 51.3–52.0%) in AC and 48.8% (95% CI, 47.8–49.8%) in MC (*Table 2*). The 5-year survival rates for each TNM stage are also shown in *Table 2*. The results of survival analysis indicate that survival rates differ between CRC subtypes most prominently in stage III and IV colon cancer patients.

Adjuvant chemotherapy for stage II SRCC colon cancer patients

For stage II SRCC colon cancer, 17.8% of the patients received 5-FU based adjuvant chemotherapy compared with 17.2% in AC. There was a significant difference in survival for AC patients between no-chemo and 5-FU groups (P<0.01), but no significant difference between 5-FU and FOLFOX groups (P=0.549) of AC patients (*Figure 2A*). However, for patients with SRCC, 5-FU and FOLFOX did not show any benefit for OS compared with the no-chemo group (P=0.067, P=0.457, respectively) (*Figure 2B*). We also verified the independent prognostic factors for OS by using a Cox proportional hazards model (*Table 3*).

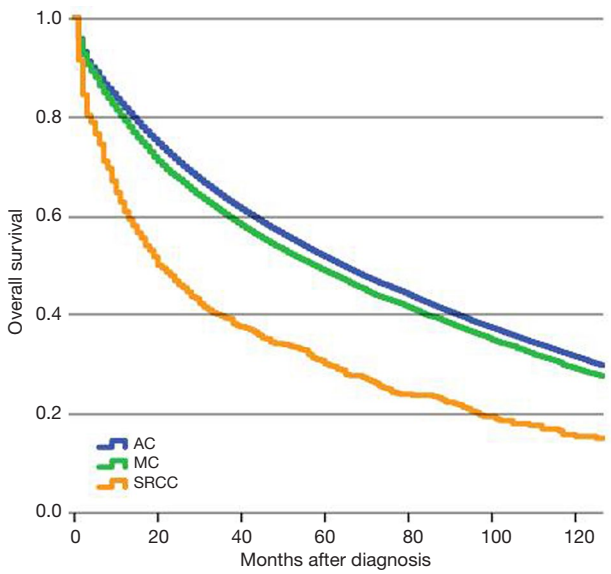

Figure 1 OS in AC, MC and SRCC patients with colon cancer. OS, overall survival; AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet-ring cell carcinoma.

PS-matched cohorts were then used to recalculate the above results. For AC group, the relevant confounding factors after PS-matched analysis of 5-FU group and no-chemo group included gender, age, race, marital status, income, level of education, primary tumor site, pT category, intestinal obstruction, intestinal perforation, HCC risk score and number of examined lymph node. The relevant confounding factors after PS-matched analysis of 5-FU group and FOLFOX group included age, marital status, income, level of education, primary tumor site, pT category, intestinal obstruction, intestinal perforation and HCC risk score. For SRCC group, there were no relevant confounding factors after PS-matched analysis of 5-FU group and no-chemo group, while race, histologic grade and intestinal perforation were included in analysis of 5-FU group and FOLFOX group. The prognosis of patients with stage II AC who received 5-FU was better than the no-chemo group (P<0.01) but was not significantly different from the FOLFOX group (P=0.799) (*Figure 2C,D*). For patients with stage II SRCC, there was still no significant prognostic difference between the no-chemo group and the 5-FU group (P=0.787) or the FOLFOX group (P=0.829) (*Figure 2E,F*).

Adjuvant chemotherapy for stage III SRCC colon cancer patients

Following surgery, 53.1% of SRCC colon cancer patients

Table 2 Five-year relative survival with 95% CI for patients with colon cancer in the US according to stage of disease and histology [1992–2009]

Stage	AC (95% CI)	MC (95% CI)	SRCC (95% CI)
I	72.3 (71.6–73.0)	69.4 (66.8–71.9)	56.2 (37.3–71.4)
II	60.2 (59.6–60.9)	62.0 (60.4–63.5)	59.2 (51.2–66.3)
III	45.3 (44.5–46.0)	42.8 (41.0–44.7)	28.0 (23.2–32.9)
IV	8.1 (7.5–8.7)	7.6 (6.3–9.1)	2.8 (1.1–6.1)
All stages	51.6 (51.3–52.0)	48.8 (47.8–49.8)	30.1 (26.7–33.5)

AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet-ring cell carcinoma.

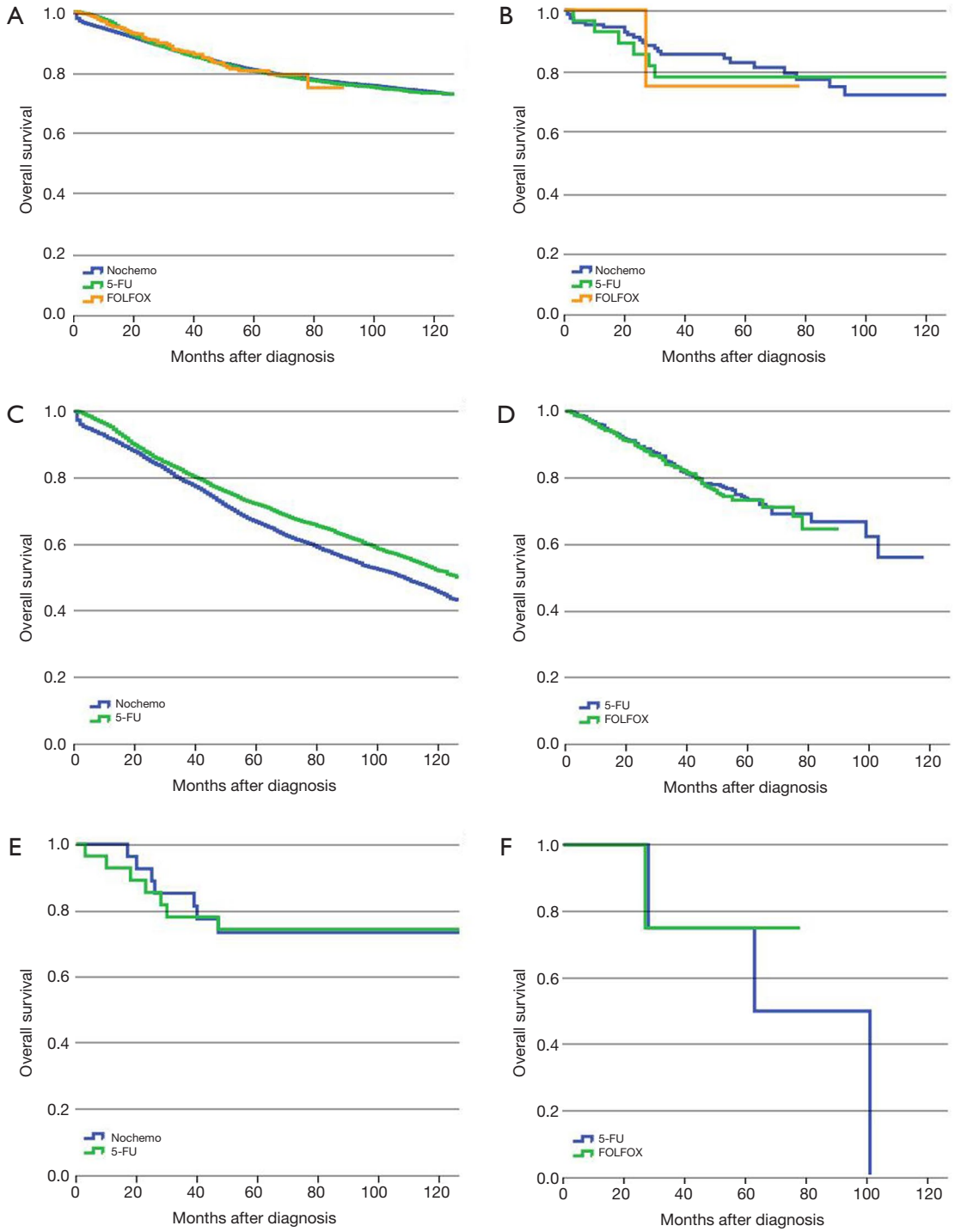

Figure 2 OS in stage II colon cancer patients with AC and SRCC. (A) OS in stage II AC patients who received surgery; (B) OS in stage II SRCC patients who received surgery; (C) after PS-match, the OS in stage II AC patients who received 5-FU regimen or not after surgery; (D) after PS-match, the OS in stage II AC patients who received 5-FU or FOLFOX regimens after surgery; (E) after PS-match, the OS in stage II SRCC patients who received 5-FU regimen or not after surgery; (F) after PS-match, the OS in stage II SRCC patients who received 5-FU or FOLFOX regimens after surgery. OS, overall survival; AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet-ring cell carcinoma; PS, propensity score.

Table 3 Multivariable analysis of factors associated with OS in stage II colon cancer patients

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender				
Male	1	–	–	–
Female	0.808 (0.777–0.840)	<0.01	–	–
Age at diagnosis, years				
<70	1	<0.01	–	–
70–74	1.333 (1.238–1.436)	<0.01	–	–
75–79	1.915 (1.783–2.057)	<0.01	–	–
80–85	2.622 (2.439–2.818)	<0.01	–	–
>85	4.483 (4.165–4.825)	<0.01	–	–
Race				
White	1	<0.01	–	–
Black	1.059 (0.992–1.130)	0.084	–	–
Asian	0.700 (0.628–0.781)	<0.01	–	–
Other	0.990 (0.899–1.091)	0.840	–	–
Marital status				
Single + separated	1	<0.01	1	0.055
Married	0.745 (0.700–0.792)	<0.01	0.898 (0.350–2.304)	0.822
Divorced + widowed	0.922 (0.867–0.980)	0.009	1.628 (0.640–4.143)	0.306
Other	0.875 (0.788–0.972)	0.013	1.921 (0.440–8.379)	0.385
Residence location				
Big metro	1	0.554	–	–
Metro or urban	0.981 (0.945–1.018)	0.306	–	–
Less urban or rural	0.979 (0.923–1.039)	0.492	–	–
Median household income				
1st quartile	1	0.223	–	–
2nd quartile	1.030 (0.976–1.085)	0.281	–	–
3rd quartile	1.038 (0.979–1.100)	0.209	–	–
4th quartile	1.075 (1.004–1.150)	0.038	–	–
Level of education				
1st quartile	1	0.060	–	–
2nd quartile	1.006 (0.956–1.059)	0.813	–	–
3rd quartile	1.031 (0.975–1.090)	0.287	–	–
4th quartile	1.086 (1.019–1.157)	0.011	–	–
Unknown	1.093 (0.988–1.210)	0.085	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
Year of diagnosis				
1992–1996	–	–	–	–
1997–2000	–	–	–	–
2001–2004	–	–	–	–
2005–2009	–	–	–	–
Primary tumor site				
Left-sided colon	1	–	–	–
Right-sided colon	0.919 (0.888–0.952)	<0.01	–	–
Histologic grade				
Well	1	0.002	–	–
Moderate	1.048 (0.983–1.118)	0.153	–	–
Poor + undifferentiated	1.128 (1.049–1.213)	0.001	–	–
Unknown	1.045 (0.909–1.201)	0.535	–	–
pT category				
pT3	1	<0.01	–	–
pT4a	1.184 (1.120–1.252)	<0.01	–	–
pT4b	1.763 (1.649–1.886)	<0.01	–	–
Intestinal obstruction				
No	1	–	–	–
Yes	1.112 (1.082–1.158)	<0.01	–	–
Intestinal perforation				
No	1	–	–	–
Yes	1.692 (1.557–1.839)	<0.01	–	–
HCC risk score				
1st quartile	1	<0.01	1	<0.01
2nd quartile	1.113 (1.057–1.173)	<0.01	1.216 (0.627–2.357)	0.563
3rd quartile	1.436 (1.366–1.509)	<0.01	0.881 (0.456–1.701)	0.705
4th quartile	2.105 (2.004–2.210)	<0.01	2.474 (1.374–4.455)	0.003
Number of examined lymph node				
<12	1	–	–	–
≥12	1.253 (1.211–1.295)	<0.01	–	–
Chemotherapy				
No	1	<0.01	1	0.528
5-FU	0.778 (0.739–0.819)	<0.01	0.708 (0.388–1.292)	0.260
FOLFOX	0.858 (0.707–1.041)	0.121	0.844 (0.114–6.271)	0.868

OS, overall survival; AC, adenocarcinoma; SRCC, signet-ring cell carcinoma.

received adjuvant chemotherapy compared with 54.5% of AC patients. The prognosis for patients with stage III AC in the no-chemo group was significantly worse than those in the 5-FU group (P<0.01). Similar results were found in SRCC patients (P<0.01). Furthermore, patients with AC who received a FOLFOX regimen had a significantly improved prognosis compared with the 5-FU group (P<0.01) (*Figure 3A*). However, we did not observe a similar survival benefit for patients with stage III SRCC receiving a FOLFOX regimen compared with a 5-FU regimen (P=0.063) (*Figure 3B*). The 5-year survival rates of SRCC patients were 18.2% (95% CI, 12.5–24.7%), 33.3% (95% CI, 25.8–41.0%) and 51.9% (95% CI, 34.0–67.2%) in no-chemo, 5-FU and FOLFOX groups, respectively. The independent prognostic factors for OS were analyzed by using a Cox proportional hazards model (*Table 4*).

Similarly, we also used the PS-matched cohorts to recalculate the above mentioned results. For patients with AC, the relevant confounding factors after PS-matched analysis of 5-FU group and no-chemo group included age, race, marital status, income, level of education, year of diagnosis, primary tumor site, histologic grade, pT category, pN category, intestinal obstruction, intestinal perforation, HCC risk score and number of examined lymph node. The relevant confounding factors of 5-FU group and FOLFOX group included gender, age, race, marital status, level of education, year of diagnosis, primary tumor site, histologic grade, pT category, pN category, intestinal obstruction, intestinal perforation and HCC risk score. For patients with stage III SRCC, the relevant confounding factors after PS-matched analysis of 5-FU group and no-chemo group included histologic grade, pT category and pN category, while age, race, pT category, pN category and intestinal obstruction were included in analysis of 5-FU group and FOLFOX group. Using PS-matched cohorts, the prognosis of stage III AC patients in the no-chemo group was significantly poorer than the 5-FU group (P<0.01) (*Figure 3C*). AC patients who received a FOLFOX regimen had a better prognosis than patients in the 5-FU group (P<0.01) (*Figure 3D*). After revising the data with PS-matched cohorts, we found that there was still a significantly different prognosis between stage III SRCC patients in the no-chemo group and the 5-FU group (P<0.01) (*Figure 3E*). Furthermore, PS-matched cohorts showed a statistically significant improvement in survival of SRCC patients in the FOLFOX group compared to 5-FU group (P=0.036) (*Figure 3F*).

Treatment for stage IV SRCC colon cancer patients

For stage IV patients, 42.1% of SRCC patients received perioperative treatment, compared to 46.8% of AC patients. The prognosis of all histological subtypes of colon cancer patients without any treatment was significantly worse than patients in other groups. For patients with AC, FOLFOX/FOLFIRI regimens could provide more of a benefit for OS than a 5-FU regimen (P<0.01). When considering FOLFOX/FOLIRI regimens, adding Bevacizumab improved the prognosis of AC patients compared to a 5-FU regimen (P<0.01), but did not improve the effect of FOLFOX/FOLIRI regimens (P=0.209) (*Figure 4A*). However, the prognostic impact of distinct regimens on the AC subtype was not completely identical to the SRCC subtype. Considering stage IV SRCC patients, there was no significant difference between the 5-FU group and FOLFOX/FOLIRI group (P=0.954), 5-FU group and Bevacizumab group (P=0.235), or FOLFOX/FOLIRI group and Bevacizumab group (P=0.187) (*Figure 4B*). A Cox proportional hazards model was also presented to verify the independent prognostic factors (*Table 5*).

Discussion

SRCC is an uncommon histological subtype of CRC, which has been reported to have a poor prognosis compared to other subtypes of CRC, such as AC and MC. In our present population-based investigation, we found that the prognosis of SRCC patients who received surgery is much worse than AC and MC patients, especially in stage III and IV patients. We also evaluated the effect of different regimens of adjuvant chemotherapy on stage II and III patients, and the effect of perioperative treatment on stage IV colon SRCC patients. The results indicated that colon SRCC patients seemed to benefit from adjuvant chemotherapy and perioperative treatment.

Currently, the main treatment for advanced colon cancer is surgery plus chemotherapy. For stage II colon cancer patients, O'Connor *et al.* analyzed whether adjuvant chemotherapy could improve OS by analyzing data from the SEER-Medicare database spanning 1992 to 2005 (16). They found that adjuvant chemotherapy did not provide a benefit for stage II colon cancer patients. Our present study demonstrated that stage II AC patients could benefit from 5-FU based adjuvant chemotherapy following resection, but there may not be a significant effect for stage II SRCC

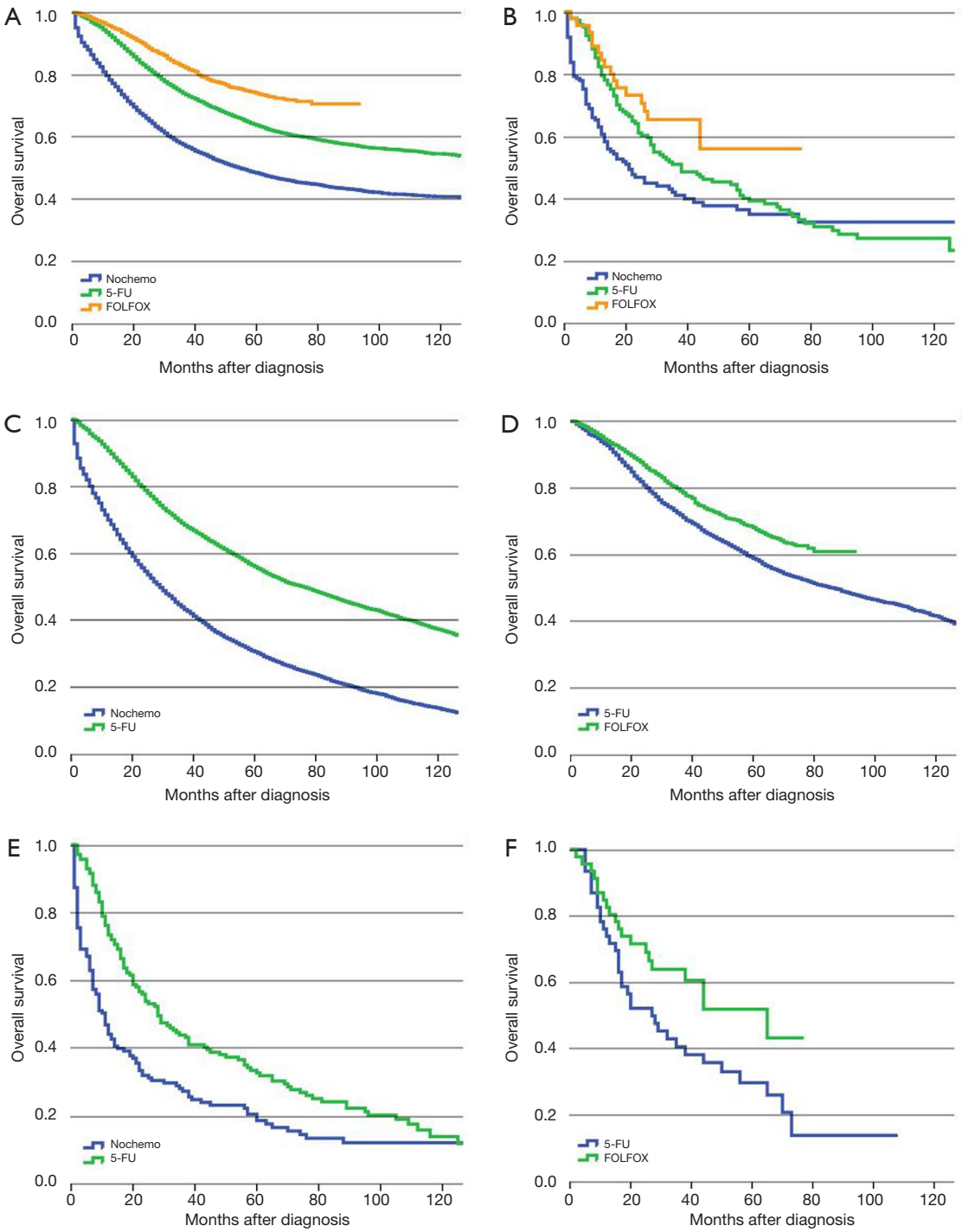

Figure 3 OS in stage III colon cancer patients with AC and SRCC. (A) OS in stage III AC patients who received surgery; (B) OS in stage III SRCC patients who received surgery; (C) after PS-match, the OS in stage III AC patients who received 5-FU regimen or not after surgery; (D) after PS-match, the OS in stage III AC patients who received 5-FU or FOLFOX regimens after surgery; (E) after PS-match, the OS in stage III SRCC patients who received 5-FU regimen or not after surgery; (F) after PS-match, the OS in stage III SRCC patients who received 5-FU or FOLFOX regimens after surgery. OS, overall survival; AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet-ring cell carcinoma.

Table 4 Multivariable analysis of factors associated with OS in stage III colon cancer patients

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender				
Male	–	–	–	–
Female	–	–	–	–
Age at diagnosis, years				
<70	1	<0.01	1	0.021
70–74	1.194 (1.115–1.278)	<0.01	0.973 (0.624–1.518)	0.904
75–79	1.451 (1.357–1.550)	<0.01	1.391 (0.892–2.169)	0.146
80–85	1.650 (1.539–1.769)	<0.01	1.729 (1.106–2.704)	0.016
>85	2.197 (2.041–2.365)	<0.01	1.600 (0.985–2.601)	0.058
Race				
White	1	<0.01	–	–
Black	1.050 (0.984–1.120)	0.141	–	–
Asian	0.664 (0.596–0.741)	<0.01	–	–
Other	0.925 (0.843–1.014)	0.095	–	–
Marital status				
Single + separated	1	<0.01	–	–
Married	0.868 (0.813–0.927)	<0.01	–	–
Divorced + widowed	0.942 (0.882–1.006)	0.076	–	–
Other	0.890 (0.791–1.002)	0.053	–	–
Residence location				
Big metro	1	–	–	–
Metro or urban	–	–	–	–
Less urban or rural	–	–	–	–
Median household income				
1st quartile	1	0.240	–	–
2nd quartile	0.973 (0.920–1.030)	0.342	–	–
3rd quartile	0.941 (0.884–1.002)	0.057	–	–
4th quartile	0.938 (0.872–1.008)	0.081	–	–
Level of education				
1st quartile	1	<0.01	–	–
2nd quartile	1.089 (1.031–1.151)	0.002	–	–
3rd quartile	1.095 (1.030–1.164)	0.004	–	–
4th quartile	1.181 (1.102–1.265)	<0.01	–	–
Unknown	1.203 (1.079–1.341)	0.001	–	–
Year of diagnosis				
1992–1996	1	<0.01	1	0.062
1997–2000	0.988 (0.936–1.041)	0.643	1.134 (0.772–1.665)	0.521
2001–2004	0.948 (0.900–0.998)	0.040	1.017 (0.704–1.468)	0.930

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
2005–2009	0.874 (0.823–0.928)	<0.01	0.684 (0.447–1.045)	0.079
Primary tumor site				
Left-sided colon	1	–	–	–
Right-sided colon	1.064 (1.024–1.105)	0.001	–	–
Histologic grade				
Well	1	<0.01	1	0.003
Moderate	1.111 (1.019–1.212)	0.017	NA	0.852
Poor + undifferentiated	1.249 (1.141–1.367)	<0.01	NA	0.830
Unknown	1.054 (0.896–1.239)	0.528	NA	0.820
pT category				
pT1	1	<0.01	1	0.111
pT2	1.127 (0.975–1.302)	0.106	NA	0.872
pT3	1.804 (1.438–2.264)	<0.01	NA	0.843
pT4a	2.194 (1.732–2.779)	<0.01	NA	0.840
pT4b	3.555 (2.746–4.603)	<0.01	NA	0.829
pN category				
pN1	1	<0.01	1	0.092
pN2	1.216 (1.164–1.270)	<0.01	1.028 (0.690–1.532)	0.891
pN3a	1.554 (1.473–1.639)	<0.01	1.512 (0.987–2.316)	0.057
pN3b	2.498 (2.255–2.766)	<0.01	1.788 (1.017–3.144)	0.043
Intestinal obstruction				
No	1	–	–	–
Yes	1.160 (1.119–1.203)	<0.01	–	–
Intestinal perforation				
No	1	–	–	–
Yes	1.520 (1.387–1.667)	<0.01	–	–
HCC risk score				
1st quartile	1	<0.01	1	0.165
2nd quartile	1.154 (1.094–1.217)	<0.01	1.095 (0.757–1.583)	0.631
3rd quartile	1.345 (1.276–1.417)	<0.01	1.346 (0.966–1.877)	0.079
4th quartile	1.754 (1.668–1.845)	<0.01	1.388 (0.984–1.958)	0.062
Number of examined lymph node				
<12	1	–	–	–
≥12	1.276 (1.229–1.324)	<0.01	–	–
Chemotherapy				
No	1	<0.01	1	<0.01
5-Fu	0.549 (0.527–0.573)	<0.01	0.497 (0.371–0.666)	<0.01
FOLFOX	0.392 (0.357–0.431)	<0.01	0.528 (0.312–0.896)	0.018

OS, overall survival; AC, adenocarcinoma; SRCC, signet-ring cell carcinoma.

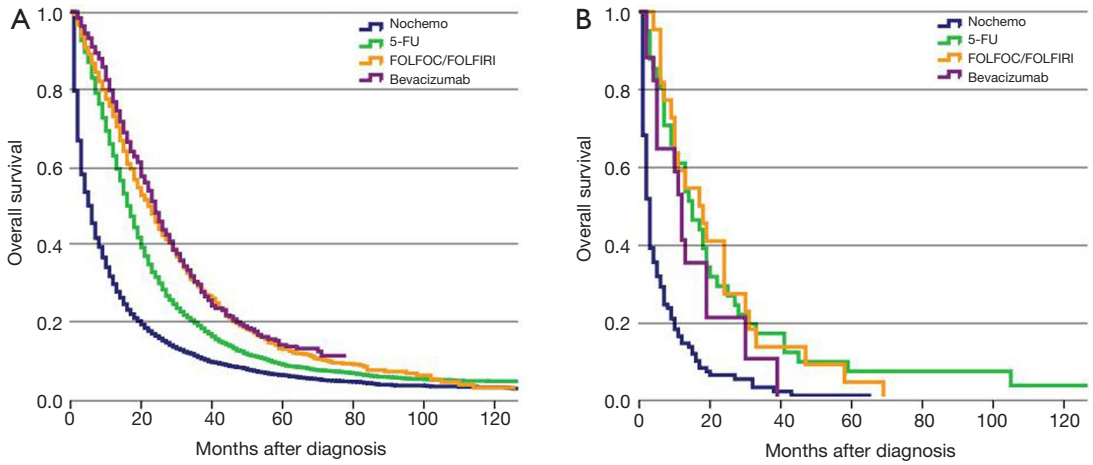

Figure 4 OS in stage IV colon cancer patients with AC and SRCC. (A) OS in stage IV AC patients who received different adjuvant therapy regimens after surgery; (B) OS in stage IV SRCC patients who received different adjuvant therapy regimens after surgery. OS, overall survival; AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet-ring cell carcinoma.

Table 5 Multivariable analysis of factors associated with OS in stage IV colon cancer patients

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender				
Male	1	–	–	–
Female	0.971 (0.924–1.020)	0.244	–	–
Age at diagnosis, years				
<70	1	<0.01	1	0.136
70–74	1.100 (1.026–1.179)	0.007	1.666 (1.032–2.690)	0.037
75–79	1.245 (1.161–1.336)	<0.01	1.907 (1.161–3.134)	0.011
80–85	1.266 (1.178–1.362)	<0.01	1.492 (0.881–2.530)	0.137
>85	1.374 (1.260–1.498)	<0.01	1.604 (0.931–2.763)	0.089
Race				
White	1	0.001	–	–
Black	1.075 (1.000–1.155)	0.050	–	–
Asian	0.796 (0.701–0.906)	0.001	–	–
Other	0.978 (0.880–1.088)	0.688	–	–
Marital status				
Single + separated	1	0.186	–	–
Married	0.933 (0.864–1.009)	0.081	–	–
Divorced + widowed	0.970 (0.897–1.050)	0.458	–	–
Other	0.911 (0.795–1.044)	0.178	–	–

Table 5 (*continued*)

Table 5 (*continued*)

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
Residence location			–	–
Big metro	1	0.802		
Metro or urban	0.994 (0.948–1.043)	0.808		
Less urban or rural	0.975 (0.903–1.051)	0.507		
Median household income			–	–
1st quartile	1	0.193		
2nd quartile	1.061 (0.993–1.134)	0.080		
3rd quartile	1.082 (1.002–1.168)	0.044		
4th quartile	1.057 (0.962–1.161)	0.247		
Level of education			–	–
1st quartile	1	0.027		
2nd quartile	0.967 (0.906–1.032)	0.308		
3rd quartile	1.008 (0.937–1.084)	0.839		
4th quartile	1.039 (0.957–1.129)	0.358		
Unknown	0.891 (0.784–1.012)	0.076		
Year of diagnosis			–	–
1992–1996	1	<0.01		
1997–2000	0.980 (0.919–1.045)	0.537		
2001–2004	0.849 (0.796–0.907)	<0.01		
2005–2009	0.682 (0.622–0.748)	<0.01		
Primary tumor site			–	–
Left-sided colon	1			
Right-sided colon	1.132 (1.084–1.183)	<0.01		
Histologic grade			–	–
Well	1	<0.01		
Moderate	1.329 (1.183–1.494)	<0.01		
Poor + undifferentiated	1.830 (1.622–2.063)	<0.01		
Unknown	1.495 (1.280–1.748)	<0.01		
pT category			–	–
pT1	1	<0.01		
pT2	1.530 (1.068–2.193)	0.020		
pT3	2.347 (1.756–3.137)	<0.01		
pT4a	3.139 (2.327–4.235)	<0.01		
pT4b	3.029 (2.249–4.079)	<0.01		

Table 5 (*continued*)

Table 5 (*continued*)

Characteristics	AC		SRCC	
	HR (95% CI)	P value	HR (95% CI)	P value
Unknown	2.479 (1.853–3.317)	<0.01		
pN category				
pN0	1	<0.01	1	0.022
pN1	1.150 (1.070–1.237)	<0.01	1.144 (0.595–2.200)	0.687
pN2	1.264 (1.187–1.346)	<0.01	0.591 (0.314–1.113)	0.104
pN3a	1.490 (1.400–1.586)	<0.01	1.254 (0.701–2.241)	0.446
pN3b	1.980 (1.857–2.110)	<0.01	1.471 (0.977–2.213)	0.064
Intestinal obstruction				
No	1	–	–	–
Yes	0.915 (0.876–0.956)	<0.01	–	–
Intestinal perforation				
No	–	–	–	–
Yes	–	–	–	–
HCC risk score				
1st quartile	1	<0.01	–	–
2nd quartile	1.014 (0.947–1.086)	0.685	–	–
3rd quartile	1.082 (1.014–1.154)	0.017	–	–
4th quartile	1.185 (1.110–1.265)	<0.01	–	–
Number of examined lymph node				
<12	1	–	–	–
≥12	1.227 (1.174–1.283)	<0.01	–	–
Chemotherapy				
No	1	<0.01	1	<0.01
5-FU	0.523 (0.497–0.551)	<0.01	0.344 (0.228–0.519)	<0.01
FOLFOX or FOLFIRI	0.478 (0.442–0.516)	<0.01	0.358 (0.216–0.593)	<0.01
Chemo + BEV	0.457 (0.416–0.503)	<0.01	0.456 (0.255–0.814)	0.008

OS, overall survival; AC, adenocarcinoma; SRCC, signet-ring cell carcinoma.

patients. Why was it different from results of stage II AC patients in SRCC group? Firstly, the sample size might be a key factor influencing the whole results. There were 22,539 patients in stage II AC group and only 180 patients in SRCC group, the small sample size of SRCC group may help explain the statistically negative results. Secondly, the molecular characteristics of colonic SRCC may be another reason causing the difference. Bellan A reported that the expression of P53 protein was down regulated in colonic SRCC cells, which means this kind of cancer cells might show resistance to chemotherapy (27,28). What's more, Pozos-Ochoa *et al*. found CK20, MUC5AC had a higher proportion of negativity in colonic SRCC cells which may cause resistance to anti-tumor drugs like 5-FU (29-31). To further investigate this issue, more researches of larger sample size and more comprehensive molecular status of

colonic SRCC patients should be done in the future.

In the 1990s, 5-FU based adjuvant chemotherapy had become the standard regimen for stage III colon cancer patients (32). In 2004, the MOSAIC trial reported that the addition of oxaliplatin to 5-FU based adjuvant chemotherapy could improve OS and disease-free survival of patients with stage III colon cancer. This finding made the FOLFOX regimen the new standard for stage III patients following resection (33). While oxaliplatin was found to increase the survival rate of CRC patients, side effects such as cytopenias, diarrhea, vomiting and peripheral neuropathy were more likely to occur with a FOLFOX regimen than with a 5-FU regimen (34). To avoid side effects brought on by adjuvant chemotherapy, regimens should be selected according to their effectiveness against specific malignancies. Therefore, we analyzed the OS of stage III colon cancer patients with different histologic subtypes to determine the effect of adjuvant chemotherapy on individual CRC subtypes. The results suggest that stage III CRC patients benefit from 5-FU based adjuvant chemotherapy after surgery and that the addition of oxaliplatin could enhance the effect of this treatment for both AC and SRCC patients. Therefore, patients with stage III colon cancer should receive standard adjuvant chemotherapy without considering histologic subtypes after surgery.

Traditionally, patients with stage IV colon cancer have received palliative systemic therapy attempting to increase OS, and palliative resections to prevent complications such as bleeding and obstruction (35,36). Recently, research from the Netherlands has suggested that patients with stage IV CRC who have received a primary tumor resection may have an improved OS compared to patients who receive systemic therapy without resection of the primary tumor (37). Hence, we performed an analysis to determine whether the histologic subtype could influence the effectiveness of systemic therapy for stage IV colon cancer patients who received surgery. The results indicated a significant survival benefit for AC patients who received surgery plus systemic therapy with 5-FU compared with AC patients who only received surgery. Furthermore, addition of oxaliplatin or irinotecan to 5-FU regimen could improve AC patients' OS compared to patients who received 5-FU only. Addition of bevacizumab did not show an enhanced benefit compared to FOLFOX/FOLFIRI regimens, which might be due to the small sample size who had received bevacizumab. Moreover, the prognosis of stage IV SRCC patients who received surgery without systemic therapy was worse than that of patients who received surgery plus systemic therapy. However, we did not observe any significant benefit among different regimens of perioperative systemic therapy for SRCC patients. From the above results, we found that patients with stage IV colon cancer should be treated with both surgery and systemic therapy if patients can tolerate the therapeutic regimens. Additionally, the histological subtypes should be considered as a factor for the prognosis and selection of therapy. Nevertheless, the above findings had some difference from the advantage of clinical trial regarding adding Bevacizumab to FOLFOX/FOLIRI. First of all, we thought that the selection of patients could be a potential concern in our present study. We extracted data of stage IV colon SRCC patients who received surgery and following systemic therapy within 9 months after resection in our work. However, in other clinical trials, some of them chose patients with metastasis but did not receive surgery or stage IV patients received resection but with different histological classifications mixed together (38,39). Thus, different patient selection among different studies might explain the different results exhibited in our present study and some clinical trials. Besides, in the Bevacizumab group, we included all patients who received Bevacizumab agent with 5-FU-based chemotherapy including 5-FU and FOLFOX/FOLFIRI regimens due to the small sample sizes. Still, many researches focusing on the efficiency of Bevacizumab for stage IV colon cancer got negative results, which may owe to the failure to comprehensively consider some important factors like the sideness of colon cancer as some studies recommended that bevacizumab treatment should preferentially go to patients with primary right-sided or left-sided colon cancer patients (40,41). The NCCN guidelines indicates that no data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease and does not recommend the use of bevacizumab for the perioperative stage IV colon cancer. We believe that more large and well-designed researches would be done and get a more solid conclusion for this issue in the future.

Our present study has some potential limitations. First, this study was a retrospective analysis, and there might be some inevitable inaccuracies in the SEER-Medicare database as it is a population-based registration database. Second, the number of patients age <65 years at the time of diagnosis was absent from our study, which influenced some results such as the relationship between the occurrence of SRCC and the ages of patients. Third, we were not able to

analyze the benefit of adjuvant chemotherapy in low-risk stage II patients, due to the low number of patients who received chemotherapy in this group. Fourth, the sample sizes, especially in SRCC groups of each stage, were not large enough for us to analyze subgroups as detailed as possible. As we tried to find whether patients with colon SRCC cancer could get benefit from adjuvant systemic therapy after surgery, there may be a selection bias hidden in the results which might cause difference between the results from our research and other clinical trials. Due to the existence of these limitations, the results of this study should be considered prudently.

Conclusions

In conclusion, we found that the prognosis of patients with colon SRCC was significantly worse than other histological subtypes. The effective role of adjuvant chemotherapy or systemic therapy for survival was shown mainly in stage III and IV SRCC patients who received surgery. In the future, histological subtypes should be individually considered during the process of therapeutic selection. However, results from randomized controlled trials are still needed to characterize the relationship between CRC subtypes and therapeutic effectiveness.

Acknowledgments

Funding: This work was supported by Clinical Capability Construction Project for Liaoning Provincial Hospitals (LNCCC-A01-2014), the Key Laboratory Programme of Education Department of Liaoning Province (LZ2015076) and National Key R & D Program of China (MOST-2017YFC0908300, MOST-2017YFC0908305).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.07.14). 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). The permission to access the research data file in SEER–Medicare program was obtained by the authors (reference no. D6-MEDIC-821). The study was approved by the Institutional Review Board of the First Hospital of China Medical University {reference no. [2012] 96}. Because the SEER-Medicare data are de-identified and are based on registry data, no prior informed consent was required.

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Cite this article as: Sun J, Wang X, Gao P, Song Y, Chen X, Sun Y, Yu D, Lv X, Wang Z. Prognosis and efficiency of adjuvant therapy in resected colon signet-ring cell carcinoma. Transl Cancer Res 2018;7(4):1006-1025. doi: 10.21037/tcr.2018.07.14

