Original Article

Basic characteristics and therapy regimens for colorectal squamous cell carcinoma

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Background: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths, and squamous cell carcinoma (SCC) is a rare histological type. Due to the lack of cases, there is no standard treatment for colorectal SCC.

Methods: In our study, we compiled data from the Surveillance, Epidemiology, and End Results Program (SEER) database between 1988 and 2014 and analyzed overall survival (OS) between groups stratified by histological type, primary tumor site or treatment regimens. The SEER-Medicare database was also used to analyze the treatment regimens in the groups stratified by tumor-node-metastasis (TNM) stage.

Results: Our results show that the colorectal SCC was commonly seen in females, and tends to have higher pT category and TNM stage. The 5-year survival rate for colorectal SCC was much lower than adenocarcinoma or mucinous adenocarcinoma and higher than signet ring cell carcinoma. Patients with rectal SCC also showed better prognosis compared with colon SCC. The colorectal patients received surgery with chemoradiotherapy or chemoradiotherapy alone have a significantly better prognosis than receiving surgery alone in SEER database. For stage I–III colorectal SCC patients who underwent an operation, chemotherapy and radiotherapy could improve the prognosis but failed to reach statistical significance, and chemotherapy is also an independent prognosis factor which could significantly improve the prognosis of stage IV colorectal SCC in SEER-Medicare database.

Conclusions: The OS rate for colorectal SCC is much lower than for adenocarcinoma and mucinous adenocarcinoma. Rectal SCC patients had better prognosis than colonic SCC.

Keywords: Squamous cell carcinoma (SCC); colorectal cancer (CRC); chemotherapy; radiotherapy

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Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in males and females worldwide (1). The incidence and mortality of CRC both rank in the top five of all cancers in China (2). Adenocarcinoma makes up more than 90% of CRC (3,4). Surgery is commonly used as the primary therapeutic regimen, and the chemoradiation would also be closed in some cases with the consideration of staging, localization, and the patient's situation (5,6).

There are several rare types of CRC tumors such as malignant carcinoid (1.5%), malignant lymphoma (0.6%), neuroendocrine carcinoma (0.3%), squamous cell carcinoma (SCC, 0.3%), and others (7). SCC is a small subset of CRC, accounting for less than 1% of CRC incidence (7,8). The incidence of rectal SCC (93.4%) is higher than colonic SCC (5.9%) (7). The most common site of SCC in the lower gastrointestinal tract is anal canal. Unlike SCC of the anal canal, colorectal SCC is much less reported. Most studies regarding colorectal SCC are limited to case reports, and the etiology is still unclear (9). There are varying hypothesizes about the etiology of colorectal SCC, such as differentiation of a pluripotent stem cell or the squamous metaplasia resulting from external irritation (10,11). Chronic inflammation or viral infection may also promote the development of colorectal SCC (9,12). However, the definite etiology of colorectal SCC remains to be discerned. Surgery was once the standard treatment for colorectal SCC, with tumor location and depth of invasion considered in operation selection (5,13). However, there is no distinct recommended treatment in the National Comprehensive Cancer Network guideline (3). In recent years, the treatment for SCC of the rectum and of the colon differs in that non-metastatic colonic SCC is only treated by surgery, while rectal SCC has the option of chemoradiotherapy with or without surgery or with surgery alone (14). Besides, there are few investigations about the treatment of the non-metastatic colonic SCC, which lacks the unified treatment standards.

In our study, we aim to compare the characteristics of colorectal SCC with different histological subtypes and different primary tumor sites using the Surveillance, Epidemiology, and End Results Program (SEER) database. We also analyze the prognosis between patients who received different therapeutic regimens using both of the SEER and SEER-Medicare linked database to help determine the optimal treatment regimen for colorectal SCC.

Methods

Data for SEER database set

This study was a retrospective investigation. Data were obtained from the SEER Program and SEER-Medicare linked databases. The study met the requirements of the SEER data use agreement. The SEER database is a population-based cancer registry accounting for approximately 28% of the US population among widespread regions, containing information including demographics, tumor characteristics, survival information, and cause of death for cancer patients.

Data for SEER-Medicare database set

For the SEER-Medicare set, this investigation was performed following the requirements of SEER-Medicare data use agreement, and approval was obtained from the First Hospital of China Medical University Institutional Review Board. The SEER-Medicare database is the primary health insurer which accounts for about 97% of the US population ≥66 years old (15).

Patients and variables for SEER database set

The World Health Organization (WHO) International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) was used to determine histological tumor types. Patients from the SEER database included in this study were diagnosed between 1988 and 2014. These patients were diagnosed with five histological types of CRC (site codes: 18.0, 18.2–18.9, 19.9, 20.9), including adenocarcinoma [8140–8147], mucinous adenocarcinomas [8480, 8481], signet ring cell carcinoma [8490], SCC [8070–8078], and adenosquamous carcinoma [8560, 8562]. The exclusion criteria for patients were: (I) a diagnosis of CRC or any other cancers within 1 year after the first admission; (II) had previous cancer diagnosis; (III) tumor-node-metastasis (TNM) stage was 0 or missing; (IV) incomplete histological type information; (V) survival time was 0 or missing.

Basic patient characteristics such as age, sex, histological grade, pathological stage, race, marital status, and diagnosis year were compared between patients with different histological types of CRC or different primary sites of SCC using data from the SEER database. Pathological stage was confirmed via the seventh edition of the Union for International Cancer Control (UICC) TNM staging system.

Patients and variables for SEER-Medicare database set

Patients from the SEER-Medicare database was aged 66 years or older and with a primary diagnosis of CRC between 1992 and 2009. All of these patients were diagnosed with colorectal (site codes: 18.0, 18.2–18.9, 19.9, 20.9) SCC [8070–8078]. The exclusion criteria for patients were: (I) a diagnosis of CRC or any other cancers within 1 year

after the first admission; (II) had previous cancer diagnosis; (III) lacked full coverage of Medicare Parts A and B from 12 months before through to 12 months after diagnosis if not dead, or were enrolled in a health maintenance organization (HMO); (IV) TNM stage was 0 or missing; (V) incomplete histological type information; (VI) survival time was 0 or missing. The detailed drug codes used in our study were based on National Drug Code and Health Care Financing Administration Common Procedure Coding System, which has been reported previously (16).

Basic patient characteristics from the SEER-Medicare database such as age, sex, histological grade, pathological stage, race, marital status, and diagnosis year were also analyzed similar to SEER dataset. Besides, residence, median household income, level of education, Hierarchical Condition Category (HCC), performing operation or not, chemotherapy, and radiotherapy were also analyzed using the SEER-Medicare database set. Centers for Medicare and Medicaid Services Hierarchical Condition Categories were used for risk adjustment, which is based on the outpatient and inpatient diagnoses from the 12 months before CRC diagnosis. The resulting score can be regarded as a prediction of patient's "future health care need" with the influence caused by the average Medicare beneficiary (HCC =1.0) (17). Pathological stage was confirmed via the seventh edition of the UICC TNM staging system.

Statistical analysis

All analyses were performed using SPSS 20.0 (Somers, NY, USA) software and R3.3.1 (Vienna, Austria). Comparisons of patient demographics and characteristics between different histological types or tumor sites were performed using the χ^2 test. To analyze the primary outcome, overall survival (OS), the Kaplan-Meier method was used. The log-rank test was used to compare survival curves. To control the influence of patient characteristics, the Cox proportional hazards model was used for the multivariate analysis. Variables which were significantly associated with survival in the univariate analysis were accepted as covariates in the Cox proportional hazards model. P values <0.05 were defined as statistically significant.

Results

Patients and tumor characteristics for SEER database set

A total of 365,202 patients were included in our study. From the SEER database, 365,098 CRC patients were included with five histological types: adenocarcinoma (n=316,835), mucinous adenocarcinoma (n=43,257), signet ring cell carcinoma (n=4,375), SCC (n=377), and adenosquamous carcinoma (n=254). We found that colorectal SCC is more common in females (64.7%) and it tends to have higher pT category and TNM stage. The most common site of colorectal SCC is the rectum (80.6%). Demographic characteristics for the five histological types are shown in *Table 1*.

Patients and tumor characteristics for SEER-Medicare database set

We included a total of 104 colorectal SCC patients from the SEER-Medicare database to investigate therapy outcomes. A higher incidence of the colorectal SCC was also seen in the females (63.5%). Besides, higher TNM stage and incidence of the rectum SCC were also found. Basic patient characteristics are shown in *Table 2*.

Survival analysis for colorectal SCC patients from the SEER database

We first analyzed 5-year survival rate for the five histological types of CRC for patients from the SEER database set using the Kaplan-Meier method. The results indicated that 5-year survival rate was significantly lower for SCC patients (35.0%, 95% CI: 29.9–40.1%) than adenocarcinoma (54.6%, 95% CI: 54.5–54.8%, P<0.001) and mucinous adenocarcinoma (51.4%, 95% CI: 50.9–51.9%, P<0.001). Furthermore, the 5-year survival rate of SCC was significantly higher than signet ring cell carcinoma (27.9%, 95% CI: 26.5–29.3%, P=0.041), and had no significant difference compared with adenosquamous carcinoma (33.7%, 95% CI: 27.7–39.9%, P=0.775, *Figure 1A*). We also compared the 5-year survival rate between five histological types of CRC stratified by TNM stage. The prognosis of the colorectal SCC patients was significantly worse than adenocarcinoma both in stage I–III patients (50.8% *vs.* 64.5%, P<0.001, *Figure 1B*) and stage IV patients (16.0% *vs.* 19.5%, P=0.002, *Figure 1C*), which was also significantly lower than mucinous adenocarcinomas both in stage I–III (50.8% *vs.* 61.0%, P=0.011, *Figure 1B*) and stage IV patients (16.0% *vs.* 17.8%, P=0.019, *Figure 1C*). Besides, the prognosis of the colorectal SCC patients was significantly better than signet ring cell carcinoma both in

Table 1 Clinicopathologic features of patients with five different histological subtypes from SEER database

Features	Squamous cell carcinoma	Adenocarcinoma	Mucinous adenocarcinoma	Signet ring cell carcinoma	Adenosquamous carcinoma	P value*
Sex						<0.001
Female	244	154,251	22,586	2,103	127	
Male	133	162,584	20,671	2,272	127	
Age at diagnosis, years						<0.001
≤57	165	77,836	10,082	1,555	88	
58–67	93	75,598	9,200	935	51	
68–77	66	85,778	12,024	952	62	
≥78	53	77,623	11,951	933	53	
Histological grade						<0.001
Well/moderate	134	240,328	29,797	284	68	
Poor/undifferentiated	176	61,541	8,901	3,441	165	
Unknown	67	14,966	4,559	650	21	
pN category						<0.001
N0	131	165,273	21,473	901	82	
N1	68	78,065	10,463	850	61	
N2	43	52,686	8,737	2,067	90	
Unknown	135	20,811	2,584	557	21	
pM category						<0.001
M0	205	247,092	33,549	2,793	156	
M1	172	69,743	9,708	1,582	98	
pT category						<0.001
T1/T2	42	61,718	6,144	290	27	
T3	145	177,846	24,130	1,950	118	
T4	79	40,136	7,689	1,294	56	
Unknown	111	37,135	5,294	841	53	
TNM stage						<0.001
I	19	46,579	4,563	157	15	
II	103	103,843	14,918	645	58	
III	83	96,670	14,068	1,991	83	
IV	172	69,743	9,708	1,582	98	
Primary tumor site						<0.001
Colon	73	233,480	36,191	3,564	177	
Rectum	304	83,355	7,066	811	77	
Diagnosis year						<0.001
1988–1998	56	76,059	11,099	805	60	
1999–2003	100	76,278	11,987	1,179	61	
2004–2008	113	79,047	10,751	1,124	64	
2009–2014	108	85,451	9,420	1,267	69	

*, P<0.05 was considered as statistically significant.

Table 2 Clinicopathologic features of patients with colorectal SCC from SEER-Medicare database

Features	Number	Percentage (%)
Sex		
Male	38	36.5
Female	66	63.5
Age at diagnosis, years		
66–72	32	30.8
73–78	21	20.2
79–85	28	26.9
>85	23	22.1
Histological grade		
Well/moderate	38	36.5
Poor/undifferentiated	45	43.3
Unknown	21	20.2
pN category		
N0	20	19.2
N1	13	12.5
N2	14	13.5
Unknown	57	54.8
pM category		
M0	14	13.5
M1	90	86.5
pT category		
T1/T2	18	17.2
T3	27	26
T4	14	13.5
Unknown	45	43.3
TNM stage		
I–III	38	36.5
IV	66	63.5
Primary tumor site		
Rectum	84	80.8
Colon	20	19.2
Diagnosis year		
1992–1998	19	18.3
1999–2002	20	19.2
2003–2006	33	31.7
2007–2009	32	30.8
Number of examined lymph node[a]		
<12	22	42.3
≥12	30	57.7
HCC risk score		
1st quartile	30	28.8
2nd quartile	15	14.4
3rd quartile	26	25
4th quartile	33	31.7
Level of education		
1st quartile	29	27.9
2nd quartile	17	16.3
3rd quartile	28	26.9
4th quartile	30	28.8
Median income		
1st quartile	32	30.8
2nd quartile	33	31.7
3rd quartile	19	18.3
4th quartile	20	19.2
Operation		
Yes	52	50
No	52	50
Residence location		
Big metro	53	51
Metro or urban	38	36.5
Less urban or rural	13	12.5
Chemotherapy		
Yes	34	32.7
No	70	67.3
Radiation		
Yes	35	33.7
No	69	66.3

[a], The lymph node harvest data of 52 patients are missing because they did not receive surgery. HCC, hierarchical condition categories; SCC, squamous cell carcinoma.

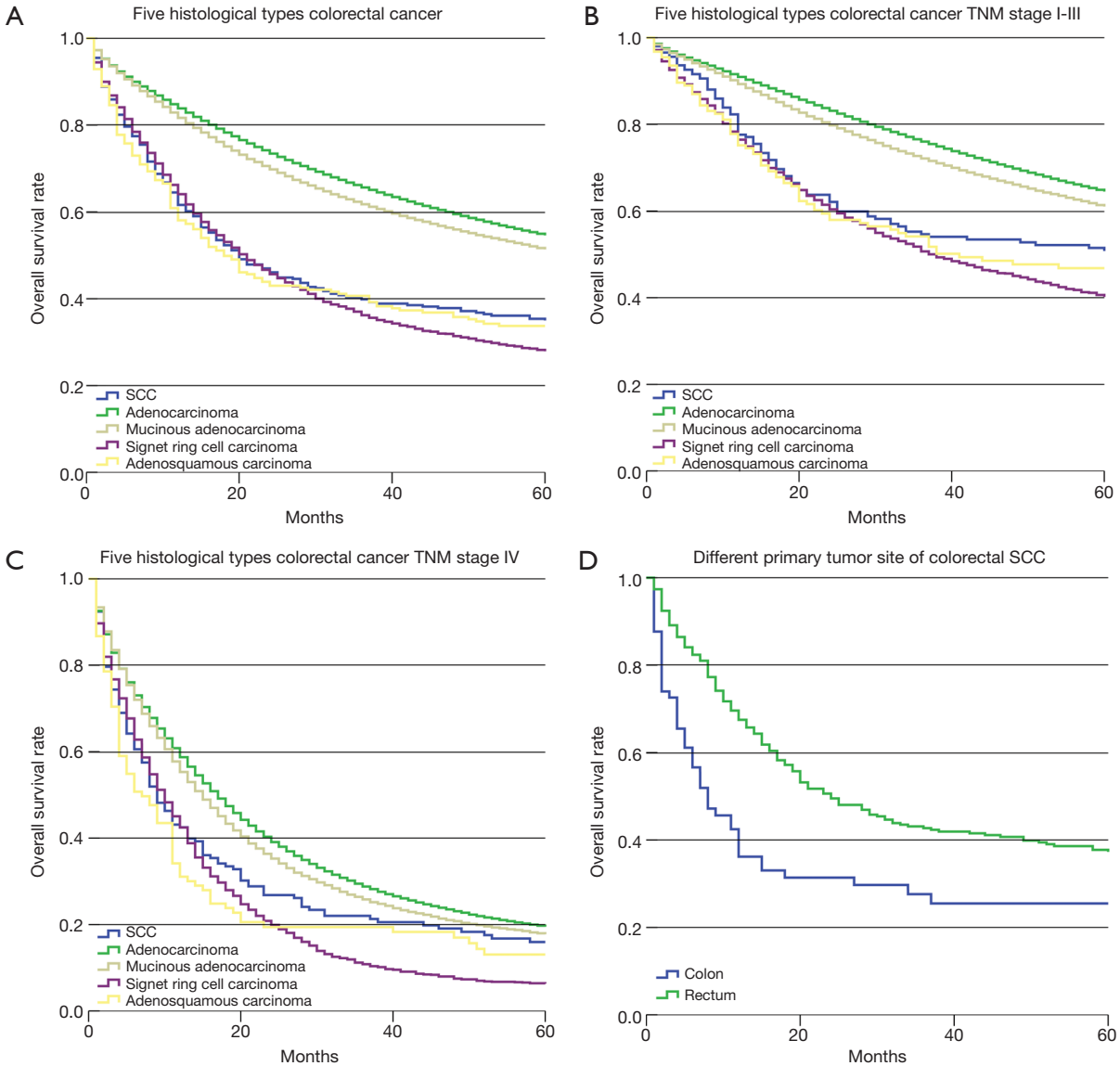

Figure 1 Five-year survival rate analysis for the patients from SEER database. (A) Five-year survival rate analysis for five histological types CRC patients; (B) 5-year survival rate analysis for five histological types CRC patients in TNM stage I–III; (C) 5-year survival rate analysis for five histological types CRC patients in TNM stage IV; (D) 5-year survival rate analysis for different primary tumor site of colorectal SCC patients. CRC, colorectal cancer; SCC, squamous cell carcinoma.

stage I–III patients (50.8% *vs.* 40.2%, P=0.005, *Figure 1B*) and stage IV patients (16.0% *vs.* 6.3%, P=0.015, *Figure 1C*). The Cox proportional hazards model was then used for the multivariate survival analysis for colorectal SCC. We found that sex and primary tumor site were independent prognosis factors for colorectal SCC, and females and patients with rectal SCC had better prognosis. Age and pM category were both independent negative prognosis factors for colorectal SCC. Details are shown in *Table 3*.

To analyze the influence of primary tumor site on prognosis, we filtered data from the SEER database, which was stratified by primary tumor site including colon and rectum. The Kaplan-Meier method was used to compare the different 5-year survival rate between these two groups. We found a significantly increasing 5-year survival rate for patients with colonic SCC (25.5%) and rectal SCC (37.3%, P<0.001, *Figure 1D*).

Table 3 Cox proportional hazards model for colorectal SCC patients from SEER database

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex				–		–
Female	1		<0.001*	1		0.008*
Male	1.636	1.264–2.117	–	1.440	1.099–1.887	–
Race						
White	1		0.118*			
Black	1.418	1.015–1.980	0.041*			
Others	0.967	0.512–1.826	0.917			
Age at diagnosis, years						
18–57	1		<0.001*	1		<0.001*
58–67	1.612	1.169–2.223	0.004*	1.635	1.170–2.284	0.004*
68–77	1.761	1.235–2.510	0.002*	1.808	1.255–2.603	0.001*
≥78	2.300	1.612–3.281	<0.001*	2.260	1.555–3.286	<0.001*
Histological grade						
Well	1		0.098			
Moderate	1.450	0.667–3.151	0.349			
Poor	1.966	0.916–4.222	0.083			
Undifferentiated	1.479	0.495–4.413	0.483			
Unknown	2.079	0.941–4.593	0.070			
pN category						
N0	1		<0.001*	1		0.124
N1	1.711	1.162–2.520	0.006*	1.552	1.035–2.326	0.033
N2	1.841	1.199–2.827	0.005*	1.404	0.875–2.251	0.160
Unknown	3.211	2.344–4.400	<0.001*	1.713	0.996–2.947	0.052
pM category						
M0	1		<0.001*	1		0.002*
M1	2.775	2.151–3.581	–	2.083	1.299–3.339	–
pT category						
T1	1		<0.001*	1		0.163
T2	2.287	0.745–7.024	0.148	2.477	0.775–7.909	0.126
T3	1.564	0.869–2.815	0.135	1.926	1.052–3.527	0.034*
T4	2.115	1.151–3.887	0.016	2.174	1.164–4.062	0.015*
Unknown	4.793	2.680–8.570	<0.001*	2.087	1.080–4.033	0.029*
Primary tumor site						
Colon	1		<0.001*	1		0.017*
Rectum	0.528	0.390–0.716	–	0.672	0.485–0.932	–

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Marital status						
Married	1		0.119			
Divorced or windowed	1.262	0.929–1.714	0.137			
Single or separate	1.451	1.065–1.978	0.018*			
Others	1.226	0.639–2.354	0.540			
Diagnosis year						
1988–1998	1		0.001*	1		0.176
1999–2003	0.824	0.578–1.175	0.286	1.157	0.799–1.676	0.440
2004–2008	0.510	0.352–0.738	<0.001*	0.789	0.526–1.186	0.255
2009–2014	0.602	0.407–0.892	0.011*	0.859	0.558–1.322	0.490

*, P<0.05 was considered as statistically significant. SCC, squamous cell carcinoma.

Treatment regiments analysis of colorectal SCC

Firstly, we divided the colorectal SCC patients from the SEER database into two groups according to TNM stage. In the stage I–III group, patients received surgery with chemoradiotherapy shared a little bit higher 5-year survival rate (56.1%) than the chemoradiotherapy alone (49.9%, P=0.767), and better than surgery along (38.7%, P=0.001) or no treatment (40.0%, P=0.365, *Figure 2A*). In stage IV patients, we also found that patients received surgery with chemoradiotherapy have the best prognosis (31.0%) among no treatment (7.8% *vs.* 31.0%, P<0.001), surgery alone (11.8% *vs.* 31.0%, P=0.004), and chemoradiotherapy alone (14.5% *vs.* 31.0%, P=0.184, *Figure 2B*). Due to the widely reported about the treatment paradigm shift of rectal SCC towards definitive chemoradiotherapy in recent years, we also analyzed the prognosis of rectal SCC patients receiving different treatment. In the stage I–III group, we found that patients received chemoradiotherapy alone shared a similar 5-year survival rate with the patients received surgery with chemoradiotherapy (54.9% *vs.* 56.5%, P=0.565), which is better than surgery alone (54.9% *vs.* 39.7%, P=0.151) and no treatment (54.9% *vs.* 40.0%, P=0.365, *Figure 2C*), but failed to reach statistical significance. In stage IV group, the rectal SCC patients receiving chemoradiotherapy alone had a significantly higher 5-year survival rate then no treatment (15.6% *vs.* 5.6%, P<0.001) and surgery alone (15.6% *vs.* 12.5%, P=0.018). However, the patients receiving chemoradiotherapy alone had a significantly lower 5-year survival rate than patients having surgery with chemoradiotherapy (15.6% *vs.* 39.4%, P=0.043, *Figure 2D*).

We also divided the colorectal SCC patients from the SEER-Medicare database into two groups according to TNM stage. In the stage I–III group, patients with no operation were excluded due to the small number. According to the Kaplan-Meier survival analysis, chemotherapy (41.6% *vs.* 26.4%, P=0.334) and radiotherapy (35.6% *vs.* 28.6%, P=0.183) could improve survival rate to some extent in stage I–III patients who underwent an operation, but failed to reach statistical significance (*Figure 3A,B*). In stage IV patients, we found that chemotherapy (20.9% *vs.* 8.1%, P=0.041) and radiotherapy (19.0% *vs.* 9.1%, P=0.029) could both obviously improve 5-year survival rate (*Figure 3C,D*). However, only chemotherapy was found to be an independent prognostic indicator for colorectal SCC patients from the results of the multivariate survival analysis (HR 3.008, 95% CI: 1.059–8.545, P=0.039). Operation performance (HR 0.359, 95% CI: 0.111–1.162, P=0.087) and radiation (HR 1.04, 95% CI: 0.272–3.975, P=0.955) did not show significant prognostic improvements from the results of the multivariate survival analysis. Besides, race and income levels were both independent prognostic indicators for colorectal SCC patients (*Table 4*).

Discussion

The diagnosis of primary colorectal SCC must meet the following requirements: the primary tumor site should be

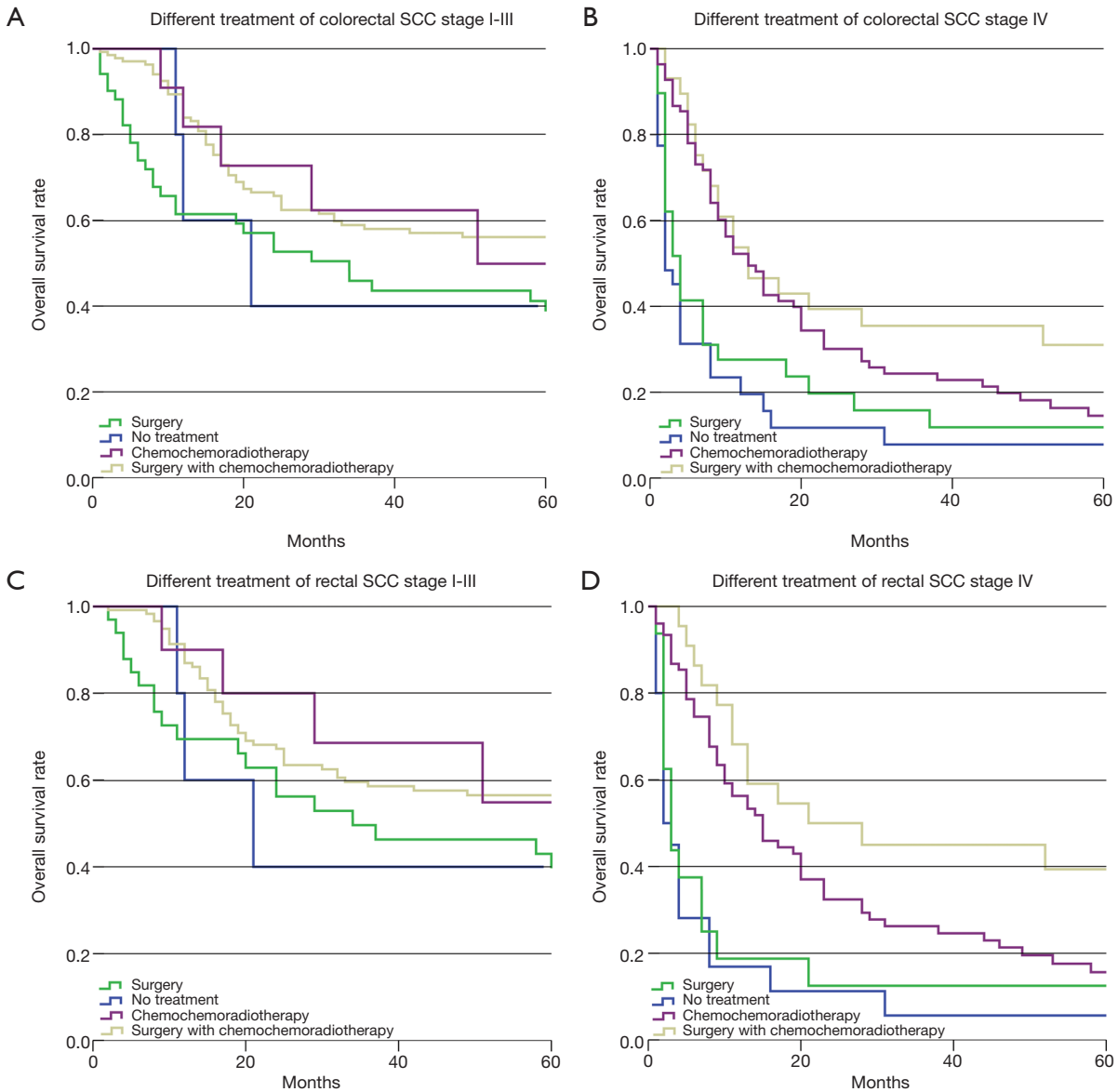

Figure 2 Five-year survival rate analysis for the colorectal SCC patients receiving different treatment regimens from SEER database. (A) Five-year survival rate analysis for TNM stage I–III colorectal SCC patients with different treatment; (B) 5-year survival rate analysis for TNM stage IV colorectal SCC patients with different treatment; (C) 5-year survival rate analysis for TNM stage I–III rectal SCC patients with different treatment; (D) 5-year survival rate analysis for TNM stage IV rectal SCC patients with different treatment. SCC, squamous cell carcinoma.

colonic or rectal, the lesions should not be involved in any squamous-lined fistula, and rectal SCC should be excluded for tumors arising from the anal squamous epithelium (11). It is widely accepted that the incidence of colorectal SCC is much lower than adenocarcinoma. For this reason, most studies on colorectal SCC are case reports (7,9,18). Details such as etiology, characteristics, and therapy guideline are still undefined for colorectal SCC.

In our study, we analyzed the characteristics of colorectal SCC using population-based data from the SEER and SEER-Medicare databases. We found that females made up a larger portion of colorectal SCC patients than males, and sex was an independent prognostic factor for colorectal SCC, similar to previous investigations (7,19). Most colorectal SCC is diagnosed with moderate or poor differentiation (75.9%), and rectal SCC (80.6%) accounts

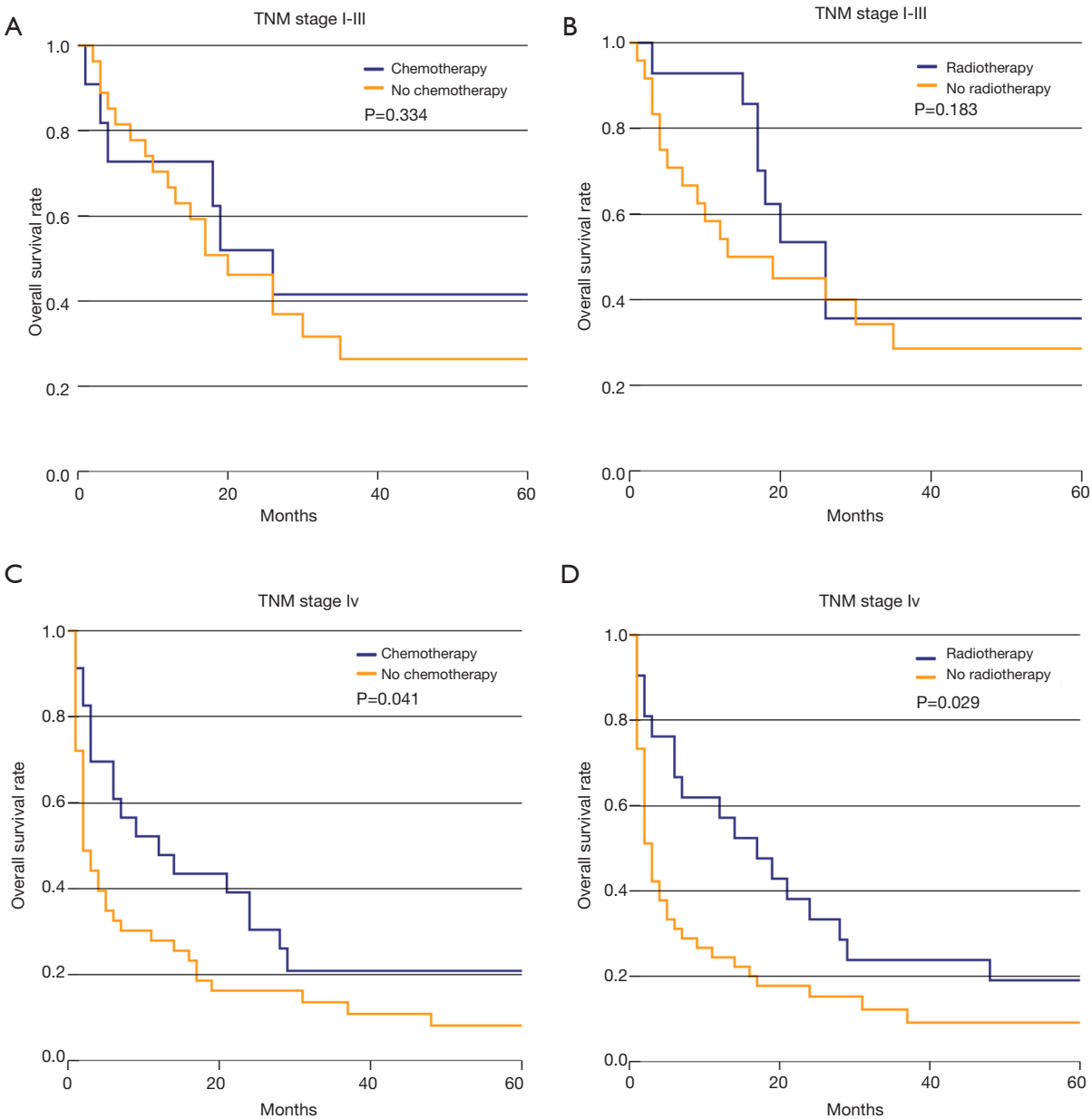

Figure 3 Five-year survival rate analysis for the patients from SEER-Medicare database. (A) Five-year survival rate analysis for TNM stage I–III colorectal SCC patients with or without chemotherapy; (B) 5-year survival rate analysis for TNM stage I–III colorectal SCC patients with or without radiotherapy; (C) 5-year survival rate analysis for TNM stage IV colorectal SCC patients with or without chemotherapy; (D) 5-year survival rate analysis for TNM stage IV colorectal SCC patients with or without radiotherapy.

for a large portion. From the survival analysis, we found that the prognosis of colorectal SCC is much worse than for adenocarcinoma (35.0% *vs.* 54.6%, P<0.001) or mucinous adenocarcinoma (35.0% *vs.* 51.4%, P<0.001), and better than ring cell carcinoma (35.0% *vs.* 27.9%, P=0.041), but no significant prognostic difference existed between colorectal SCC and adenosquamous carcinoma. Masoomi *et al.* similarly found that SCC had a higher mortality than adenocarcinoma (20). There are some factors may affect the prognosis of colorectal SCC. First of all, the rectal SCC may have a higher propensity for frequently locally invasive and metastatic dissemination when compared with

Table 4 Cox proportional hazards model for colorectal SCC patients in stage IV from SRRE-Medicare database

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Male	1		–	1		–
Female	0.615	0.361–1.049	0.074	0.505	0.183–1.39	0.186
Race						
White	1		0.097	1		0.049*
Black	1.726	0.839–3.552	0.138	3.676	0.947–14.273	0.06
Asian	5.812	0.753–44.847	0.091	11.517	0.625–212.177	0.1
Other	3.009	0.711–12.734	0.135	10.939	0.61–196.112	0.104
Age at diagnosis, years						
66–72	1		0.787	1		0.534
73–78	0.855	0.384–1.907	0.702	0.806	0.248–2.617	0.719
79–85	1.175	0.592–2.333	0.645	1.337	0.451–3.961	0.601
>85	1.251	0.601–2.603	0.549	2.095	0.563–7.792	0.27
Histological grade						
Well	1		0.219	1		0.153
Moderate	1.624	0.215–12.288	0.638	0.885	0.037–21.29	0.94
Poor	2.843	0.381–21.228	0.308	2.286	0.133–39.394	0.569
Undifferentiated	10.901	0.65–182.916	0.097	20.355	0.257–1614.901	0.177
Unknown	2.092	0.279–15.714	0.473	1.992	0.106–37.604	0.646
Primary tumor site						
Rectum	1		–	1		–
Colon	1.775	0.902–3.495	0.097	3.222	0.874–11.883	0.079
Marital status						
Single or separate	1		0.623	1		0.726
Married	1.354	0.658–2.785	0.41	0.96	0.285–3.229	0.947
Divorced or windowed	0.879	0.467–1.657	0.691	1.634	0.595–4.492	0.341
Other	0.816	0.237–2.813	0.747	0.922	0.155–5.481	0.929
Year at diagnosis						
1992–1998	1		0.432	1		0.466
1999–2002	1.315	0.505–3.425	0.575	0.211	0.031–1.44	0.112
2003–2006	0.74	0.327–1.675	0.47	0.414	0.075–2.3	0.314
2007–2009	0.715	0.305–1.676	0.441	0.463	0.087–2.469	0.368

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
HCC risk score						
1st quartile	1		0.505	1		0.598
2nd quartile	1.341	0.567–3.171	0.504	0.924	0.289–2.956	0.894
3rd quartile	1.779	0.846–3.742	0.129	1.957	0.653–5.867	0.231
4th quartile	1.43	0.702–2.913	0.324	1.506	0.49–4.626	0.475
Level of education						
1st quartile	1		0.900	1		0.281
2nd quartile	1.05	0.465–2.368	0.907	2.096	0.634–6.929	0.225
3rd quartile	1.138	0.555–2.335	0.724	2.741	0.783–9.596	0.115
4th quartile	1.297	0.638–2.636	0.472	0.778	0.195–3.104	0.722
Median income						
1st quartile	1		0.434	1		0.037*
2nd quartile	0.643	0.329–1.254	0.195	0.383	0.094–1.554	0.179
3rd quartile	0.55	0.241–1.257	0.156	1.179	0.282–4.932	0.822
4th quartile	0.719	0.356–1.452	0.357	3.722	0.864–16.024	0.078
Residence location						
Big metro	1		0.639	1		0.095
Metro or urban	1.171	0.665–2.065	0.584	1.395	0.544–3.579	0.488
Less urban or rural	1.44	0.653–3.173	0.366	6.995	1.191–41.098	0.031
Chemotherapy						
Yes	1		–	1		–
No	1.727	0.983–3.034	0.058	3.008	1.059–8.545	0.039*
Radiation						
Yes	1		–	1		–
No	1.813	1.019–3.225	0.043*	1.04	0.272–3.975	0.955
Operation						
Yes	1		–	1		–
No	0.829	0.429–1.601	0.576	0.359	0.111–1.162	0.087

*, P<0.05 was considered as statistically significant. HCC, hierarchical condition categories; SCC, squamous cell carcinoma.

adenocarcinoma, which may probably cause by a delayed diagnosis (21,22). Thus, the locally invasion and metastasis would contribute to the poor prognosis of colorectal SCC. Besides, the recent studies have given a global paradigm shift from surgery towards definitive chemoradiotherapy to improve the rectal SCC patients' prognosis. However, some investigators reported that rectal SCC may be less radiosensitive than its histologic counterparts, which may lead to a worse prognosis (3).

We also analyzed survival rates between different primary

tumor sites, finding a significantly increasing 5-year survival rate among colonic and rectal SCC (25.5% *vs.* 37.3%, P<0.001). The five-year survival rate for the squamous cell rectal cancer among the literature have varied from 32–86%, which limited by small sample size (3,7,23-25). In our study, the 5-year survival rate was lower than many of studies, which may be caused by the following reasons. Firstly, the ratio of the stage IV patients in our study was higher (45.6%). The 5-year survival rate of stage I–III rectal SCC patients was 52.3%, which was much higher than stage IV patients (18.2%). Kang *et al.* also reported that the 5-year survival rate of the stage IV patients was 20.8%, which was lower than other stages (7). Therefore, the heavy preponderance of stage IV patients may also lead to the poor prognosis of rectal SCC. Secondly, we included the patients diagnosed in a long-time span [1988–2014] from the SEER database, and the 5-year survival rate are different among different periods (19.6% for 1988–1998 group, 39% for 1999–2003 group, 45.3% for 2004–2008 group, 35.4% for 2009–2014 group). The treatment efficiency of the rectal SCC was unsatisfied in the early years, which has been improved in recent years. Kulaylat *et al.* has reported that the 5-year survival rate of the rectal SCC patients was 66.8% who was diagnosed between 2006–2012 (3). Besides, Kang *et al.* also reported the 5-year survival rate of the colorectal SCC patients diagnosed between 1991 and 2000 was 48.9%, which is much lower than Kulaylat's result (7). Thus, the different period has the different treatment regimens, which may lead to the different prognosis of rectal SCC patients.

No optimal therapy regimens have been established for colorectal SCC due to its low incidence. For rectal SCC, surgery was once the standard treatment, with tumor location and depth of invasion considered in operation selection (4,13). With medical advancements, chemoradiotherapy has gradually been accepted as the standard treatment for anal SCC since their introduction by Nigro in the 1970s (26). These findings strongly influenced the treatment of rectal SCC. Thus, many investigations have evaluated its therapeutic efficacy, showing that chemoradiotherapy could lead to higher local control rate, longer survival time, and a high rate of organ preservation for rectal SCC (24,27). However, some studies still reported that surgery was useful to help improve survival rates for rectal SCC (23,28). Besides, the current literature of colorectal SCC consists primarily of case reports, case series, and lacks the large population-based study. Thus, the treatment for colorectal SCC is still controversial. From the SEER database, we found that colorectal SCC patients received surgery with chemoradiotherapy treatment had a higher 5-year survival rate than surgery alone and chemoradiotherapy alone. For stage I–III rectal SCC patients, patients received chemoradiotherapy alone shared a similar 5-year survival rate than surgery with chemoradiotherapy treatment (54.9% *vs.* 56.5%, P=0.565), which is better than surgery alone (39.7%, P=0.151), but failed to reach statistical significance. In stage IV group, the rectal SCC patients receiving chemoradiotherapy alone had a significantly higher 5-year survival rate then no treatment and surgery alone. In SEER-Medicare database, we found that most stage I–III patients underwent surgery. In these patients, chemotherapy (41.6% *vs.* 26.4%) and radiotherapy (35.6% *vs.* 28.6%) improved the 5-year survival rate, though not with statistical significance, possibly due to the limited patient numbers. For stage IV patients, chemotherapy was an independent prognosis factor (HR 3.008, 95% CI: 1.059–8.545, P=0.039). In conclusion, the chemoradiotherapy may improve the prognosis of the colorectal SCC patients.

Although we have analyzed the characteristics of colorectal SCC from different angles, there are still many limitations. First, our study is retrospectively, and the SEER database only represents less than a third of the US population. The results may be biased in terms of socioeconomic and other factors. Second, the small number of colorectal SCC patients in some groups prevents us from performing a deeper investigation delineating the optimal treatment for colorectal SCC. Third, the results of the SEER database identifies the 18–57 years old age group as the highest incidence group, and the patients in SEER database were diagnosed between 1988 and 2013. However, the SEER-Medicare database only contains patients older than 65 years and diagnosed between 1992 and 2009. These differences would introduce significant bias when attempting to assess the effect of treatment regimen. Fourth, there is a heavy preponderance of stage IV patients in our study, which indicates that many of the operation may have been undertaken with a palliative rather than curative intent, which had a great impact on patients' outcomes and the results. Fifth, stage I–III patients with no operation were excluded due to the small number in the SEER-Medicare database, which is unusual given the paradigm shift in the treatment of rectal SCC towards definitive chemoradiotherapy in recent years. However, many patients in our study have an unclear TNM stage because they did not receive operation, and have been excluded according

to the exclusion criteria of our study. Besides, the included patients were diagnosed between 1992 and 2009 in the SEER-Medicare database. The treatment paradigm for SCC of the rectum primarily involves surgery in that period. Thus, most of the stage I–III patients received an operation in our study. In conclusion, further multi-center, large population-based analyses should be performed to clarify guidelines for the treatment of colorectal SCC.

Conclusions

Our study shows that the 5-year survival rate for colorectal SCC is much lower than adenocarcinoma or mucinous adenocarcinoma, and similar to signet ring cell carcinoma and adenosquamous carcinoma. Patients with rectal SCC had a better prognosis compared with colon SCC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.03.04). 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). Review by the institutional review board was not required for this study as the SEER database is publicly available without individually identifiable private information. Informed consent was waived.

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