Original Article

Clinicopathological features and prognostic analysis of signet ring cell gastric carcinoma: a population-based study

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Background: The impact of signet ring cell carcinoma (SRC) on gastric cancer patients' prognosis remains controversial. The aim of this study was to evaluate the clinicopathological characteristics and prognosis of SRC carcinoma and adenocarcinoma (AC) in patients with gastric cancer (GC).

Methods: An electronic search of SRC and AC cases from 2004 to 2015 was conducted within the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database. According to histological type, AC patients were divided into two groups: well- and moderately differentiated (WMD) and, poorly differentiated adenocarcinoma (PD). Kaplan-Meier (KM) curves were used to compare 5-year overall survival (OS), Univariate, and multivariable analysis were performed by Cox regression model.

Results: We identified 29,851 gastric cancer patients, among whom 16,482 were in the M0 group and 13,369 were in the M1 group. SRC patients had younger age distribution and were more seen in women. SRC was more likely to be found in advanced T and N stage, and with more distant metastasis. The most common metastatic site was bone-in SRC, while the most common site was the liver for WMD and PD. In the M0 group, multivariable analyses demonstrated that SRC had a similar survival rate with WMD and PD in stage I, and with the stage increasing, the overall survival of SRC was worse than that of WMD. Meanwhile, in the M1 group, SRC had an even worse prognosis than PD.

Conclusions: SRC was significantly different from AC in its clinicopathologic characteristics. Although the prognosis of SRC was similar to AC in the early stage, it had a more inferior prognostic impact with the progression of the disease. Different therapeutic regimens and imaging evaluations should be applied according to the histological types of gastric cancer.

Keywords: Gastric signet ring cell carcinoma; adenocarcinoma; clinicopathological features; prognosis

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Introduction

Gastric cancer is the fifth most common cancer in the world and is the third leading cause of cancer mortality (1). Histologically, gastric cancer exhibits obvious heterogeneity at the constructional and cytological levels and usually coexists with several histological components (2). Signet ring cell gastric carcinoma is a histological diagnosis based on microscopic characteristics as described by the World Health Organization (3). Gastric signet ring cell carcinomas (SRCs) are described as being isolated or a micro-community of malignant cells with intracytoplasmic mucins accounting for more than 50% of the tumors (3). In

other classifications, it is classified into "diffuse-type" in the Lauren, "anaplastic carcinoma" in Japan, and "infiltrative type" in the Ming classification. It is generally believed that the biological behaviors of SRC differ from that of other histological types. However, the reports of clinicopathologic features and prognostic impacts were still inconsistent. Some studies reported that the long-term survival rate of SRC was better than that of the AC type in early GC (4). Others revealed no significant differences between them (5-7) or whether or not SRC had a worse prognosis (8) in advanced GC. Therefore, to better understanding the prognostic impact of SRC, it is necessary to include a larger volume of patients with consistency in pathological diagnosis. This study aimed to retrospectively estimate the differences in the clinicopathological characteristics and the overall survival of SRC when compared to WMD and PD in patients with gastric cancer.

Methods

Patient selection

Data was collected from the SEER Regs Custom Data (with additional treatment fields), Nov 2017 Sub (1973–2015 varying) (https://seer.cancer.gov/). This study analyzed records from 2004 to 2015. The pT, pN, and pM of records were determined respectively with SEER data, which included collaborative stage extension (2004+), collaborative stage (CS) regional nodes positive (1988+), and CS metastases (mets) at distant sites (dx) (2004+). The American Joint Committee on Cancer (AJCC) staging manual (8th edition) was used to restage cases from this duration, and patients with less than 15 nodes dissected were classified as pNx. SRC was defined by WHO classification as an adenocarcinoma containing intra-cellular mucin comprising more than 50% of the tumors in the SEER database. Patients between 20 and 70 years, with a pathologic confirmation of gastric signet ring cell carcinoma and gastric adenocarcinoma were included. The International Classification of Diseases code M-8490/3 was used for patients with signet ring cell gastric carcinoma, and codes M-8140/3, M-8145/3, M-8210/3, M-8211/3, M-8255/3, M-8260/3, M-8263/3, M-8310/3, M-8323/3, M-8480/3, M-8481/3 were used to identify adenocarcinoma. Exclusion criteria were as follows: patients with unknown vital status, unknown metastatic status, undifferentiated and unknown histological type, and who died within 1 month. Additionally, in terms of the M0 group, patients not undergoing surgery or unknown surgery status, with no lymph node examined, an unknown number of positive lymph nodes, and unknown T stage were excluded. Due to small population sizes (N=1,117) in well-differentiated AC, patients were divided into three groups: SRC, WMD, and PD for further analysis. The primary endpoint was determining the 5-year overall survival (OS).

Statistical analysis

The demographic and clinical characteristics were compared among groups by independent *t*-test and χ^2 tests. The Kaplan Meier (KM) method was used to generate the survival curves, and then the log-rank test was performed. Long-term survival was assessed using the 5-year overall survival rate. Cox regression hazard model was used for univariable and multivariable analysis. Subgroup analysis of OS in each stage were displayed using forest plot. Prognostic factors consisted of histological type; age at diagnosis; gender; race; T and N stage; distant metastasis; metastasis to bone, brain, liver, and lung; tumor size; tumor site; and presence of radiation therapy. A $P<0.05$ value was considered as statistically significant for all analyses. All data analyses were performed by SPSS version 23.0 and Stata 12.0.

Results

Patient demographics

A total of 29,851 patients diagnosed with AC or SRC were analyzed, of whom 16,482 were patients absent from distant metastasis and who received gastrectomy (M0 group); 13,369 had distant metastasis (M1 group). A consort diagram is shown in *Figure 1*. As shown in *Table 1*, of the M0 group, 3,715 patients were recorded as SRC, and 12,767 patients were recorded as AC. Of these AC patients, 5,312 were well- and moderately differentiated, while 7,455 were PD. The age at diagnosis was younger in the SRC patients than in the WMD or PD patients (SRC: 60 yrs; WMD: 66 yrs; PD: 63 yrs; SRC *vs.* WMD and PD: *t*-test $P<0.001$). SRC had a higher proportion of females (SRC: 47.4%; WMD: 27.2%; PD: 34.0%; χ^2 test $P<0.001$). In the M1 group, 4,059 patients were with SRC, 2948 were WMD, and 6,362 were PD. The demographics were similar to the M0 group, SRC patients were younger (SRC: 57 yrs; WMD: 64 yrs; PD: 61 yrs; SRC *vs.* WMD and PD: *t*-test $P<0.001$) and more were female (SRC: 50.3%; WMD:

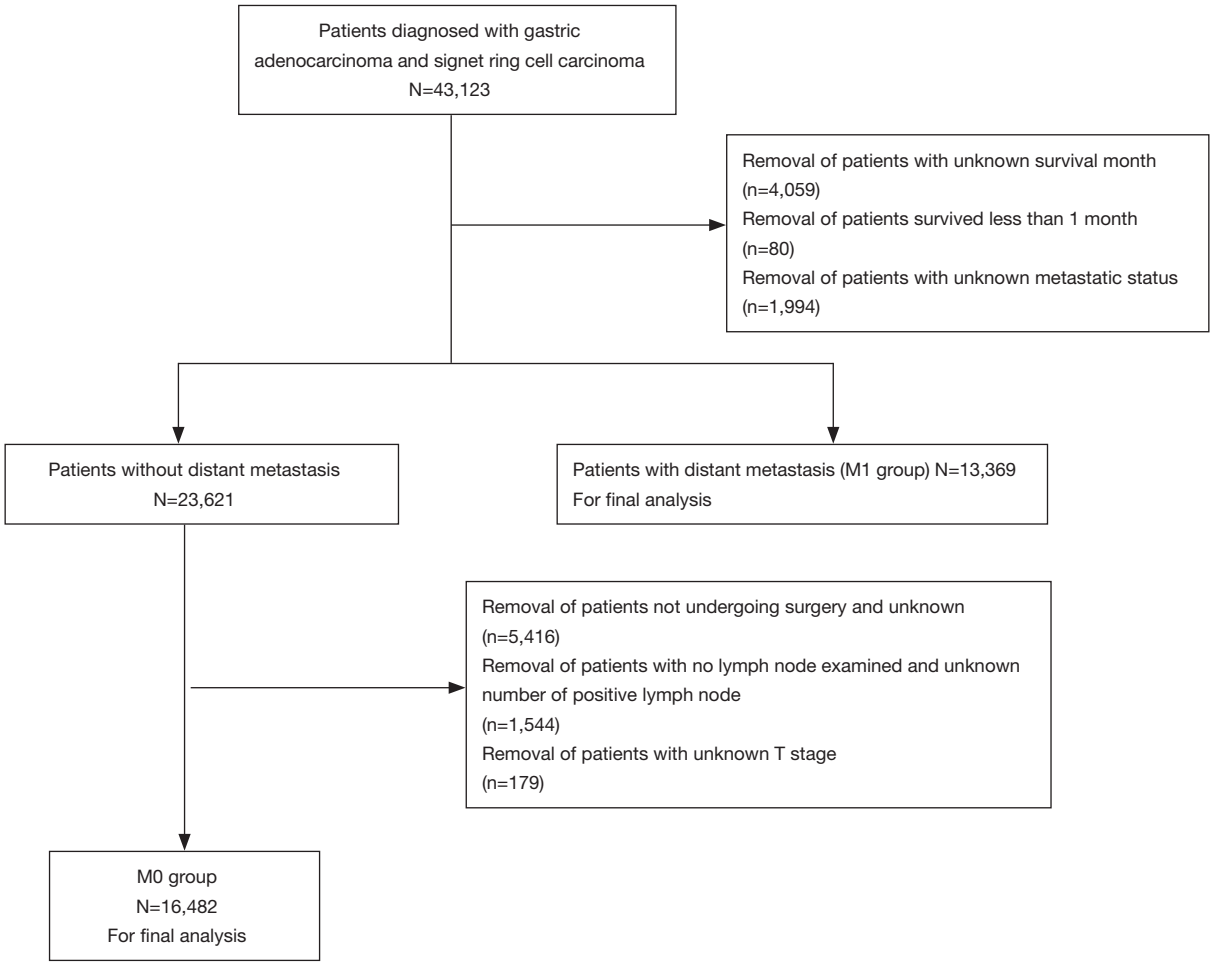

Figure 1 Consort diagram. AJCC, American Joint Committee on Cancer, 8th edition.

35.7%; PD: 32.1%; χ^2 test P<0.001) (*Table S1*).

Tumor features

In the M0 group, SRC was more frequently in the lower stomach (gastric antrum and pylorus) while AC was found mostly in the upper third of the stomach (cardia and gastric fundus). A higher percentage of patients with signet ring cell carcinoma was also likely in overlapping type (13.5% *vs.* 4.7% *vs.* 9.2%; P<0.001). More signet ring cell carcinoma presented with tumor stages T4a and T4b (35.6% *vs.* 28.5% *vs.* 33.4%; P<0.001). A higher rate of patients was diagnosed with node stages N3a and N3b in the SRC type (41.3% *vs.* 15.2% *vs.* 35.3%; P<0.001) (*Table 1*). Signet ring cell carcinoma patients was more common in AJCC stage IV (52.2% *vs.* 24.9% *vs.* 46.0%; P<0.001). In the M1 group, SRC had no significant difference from PD in tumor features, except that SRC was with more advanced T (P<0.001). While compared with WMD, SRC also had more advanced T (P<0.001) and node stage (P=0.014) and was more common in the overlapping type (P<0.001) (*Table S1*).

Metastatic patterns of SRC, WMD, and PD were further evaluated. The distant metastasis of SRC was most common in the bone (46.1%), and the liver was the most common metastatic site in patients with WMD (64.7%) and PD (55.9%) (*Figure 2A*), while a brain metastasis was least common all the histological types. There was no significant difference in the number of metastatic sites between SRC and WMD (P=0.173) or PD (P=0.181) (*Table 2*), but SRC tended to have fewer multiple metastases (SRC *vs.* WMD *vs.* PD: 19.1% *vs.* 22.4% *vs.* 22.6%; P=0.117 and 0.068, respectively) (*Figure 2B*).

Table1 Clinicopathological features of M0 group

Variables	Signet ring cell carcinoma (A) (N=3,715)		Well and moderately differentiated AC (B) (N=5,312)			Poorly differentiated AC (C) (N=7,455)		
	N	%	N	%	P (A *vs.* B)	N	%	P (A *vs.* C)
Age (yrs)					<0.001			<0.001
Mean	60		66			63		
SD	12.2		9.8			10.9		
Gender					<0.001			<0.001
Male	1,954	52.6	3,866	72.8		4,919	66	
Female	1,761	47.4	1,446	27.2		2,536	34	
Race					0.018			0.749
White	2,460	66.5	3,579	67.6		4,892	65.8	
Black	484	13.1	755	14.3		989	13.3	
Other[a]	754	20.4	963	18.2		1,553	20.9	
AJCC stage					<0.001			<0.001
I	412	21.0	869	37.4		642	16.8	
II	432	22.0	728	31.4		1,051	27.5	
III	1,119	57.0	725	31.2		2,133	55.8	
T stage					<0.001			<0.001
T1	816	22	1,897	35.7		1,250	16.8	
T2	367	9.9	806	15.2		889	11.9	
T3	1,210	32.6	1,627	30.6		2,829	37.9	
T4a	1,020	27.5	750	14.1		1,938	26	
T4b	302	8.1	232	4.4		549	7.4	
Node stage					<0.001			<0.001
N0	625	31.8	1,250	53.8		1,108	29.0	
N1	228	11.6	389	16.8		621	16.2	
N2	300	15.3	329	14.2		743	19.4	
N3a	438	22.3	274	11.8		828	21.6	
N3b	372	19.0	80	3.4		526	13.7	
Examined LN					<0.001			0.130
≥15	1,963	52.8	2,322	43.7		3,826	51.3	
<15[b]	1,752	47.2	2,990	56.3		3,629	48.7	
Tumor location					<0.001			<0.001
Upper stomach	695	26.4	2,282	53.1		2,520	43.6	
Middle stomach	402	15.2	392	9.1		696	12.1	
Lower stomach	1,185	44.9	1,420	33		2,028	35.1	
Overlapping	355	13.5	203	4.7		531	9.2	
Tumor size (cm)					<0.001			0.230
≥5	1,324	42.8	1,525	31.9		2,923	55.9	
<5	1,770	57.2	3,254	68.1		3,707	44.1	

yrs, years; SD, standard deviation; LN, lymph node; AJCC, American Joint Committee on Cancer. [a]includes American Indian/AK Native, Asian/Pacific Islander; [b]examined lymph nodes <15 was defined as pNx.

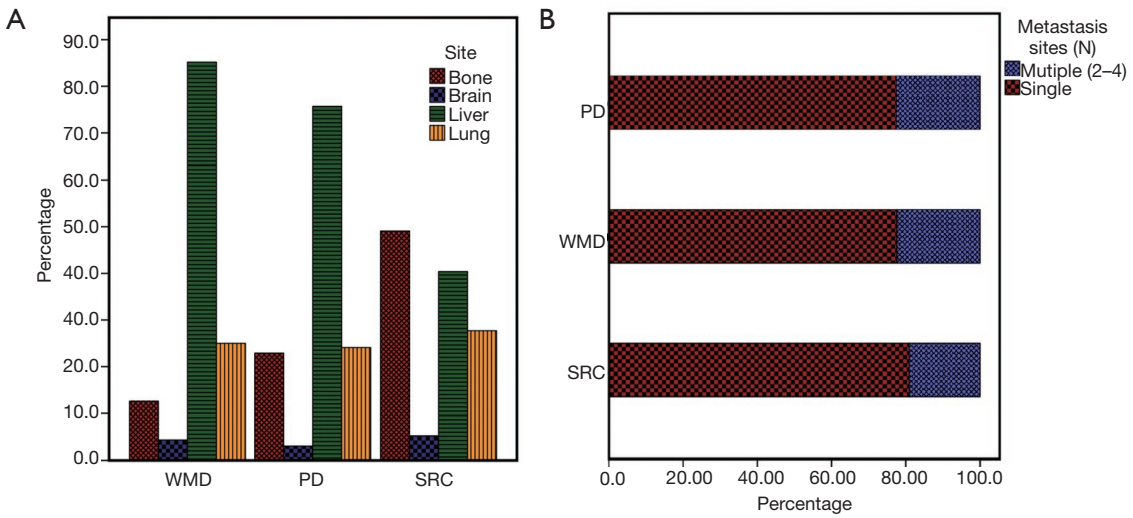

Figure 2 Metastatic pattern of well-to-moderately differentiated (WMD) and poorly differentiated (PD) and signet ring cell carcinoma (SRC) (A) metastatic sites; (B) the number of metastatic sites.

Table 2 Metastasis pattern of different histological types

Characteristics	SRC (A)		WMD (B)		PD (C)	
	N (%)	P value (A *vs.* B)	N (%)	P value (B *vs.* C)	N (%)	P value (A *vs.* C)
Metastasis site		<0.001		<0.001		<0.001
Bone	316 (40.1)		143 (9.9)		430 (18.2)	
Brain	34 (4.3)		50 (3.5)		58 (2.5)	
Liver	260 (33.0)		968 (67.0)		1,421 (60.2)	
Lung	178 (22.6)		284 (19.7)		452 (19.1)	
Number of metastasis sites		0.173		0.023		0.181
One	520 (80.9)		882 (77.6)		1,452 (77.4)	
Two	103 (16.0)		201 (17.7)		371 (19.8)	
Three	18 (2.8)		51 (4.5)		49 (2.6)	
Four	2 (0.3)		2 (0.2)		5 (0.3)	

SRC, signet ring cell carcinoma; PD, poorly differentiated; WMD, well-to-moderately differentiated.

Survival

To avoid the impact of inadequately examined LN on the N stage, we only conducted the survival analysis among patients with an examined LN >15 in the M0 group. KM curves, according to histological classification, are shown in *Figure 3*. In the M0 group, the overall survival of SRC and AC significantly differed (36.7 *vs.* 40.0 months, respectively; log-rank P<0.001) (*Figure 3A*). We then divided the non-SRC into WMD and PD groups and compared the OS of SRC with these two groups. SRC demonstrated significantly worse OS than WMD and PD (P1<0.001; P2=0.863; P3<0.001) (*Figure 3B*). However, in stage I (*Figure 4A*), SRC was shown to have a better prognosis than WMD and PD. While in stage II, SRC had a similar survival with PD, and both showed worse OS than WMD (*Figure 4B*). SRC had worse survival than WMD and PD in stage III (*Figure 4C*). In the M1 group, SRC demonstrated significantly worse survival than AC (*Figure 3C*). SRC also had a worse prognosis than

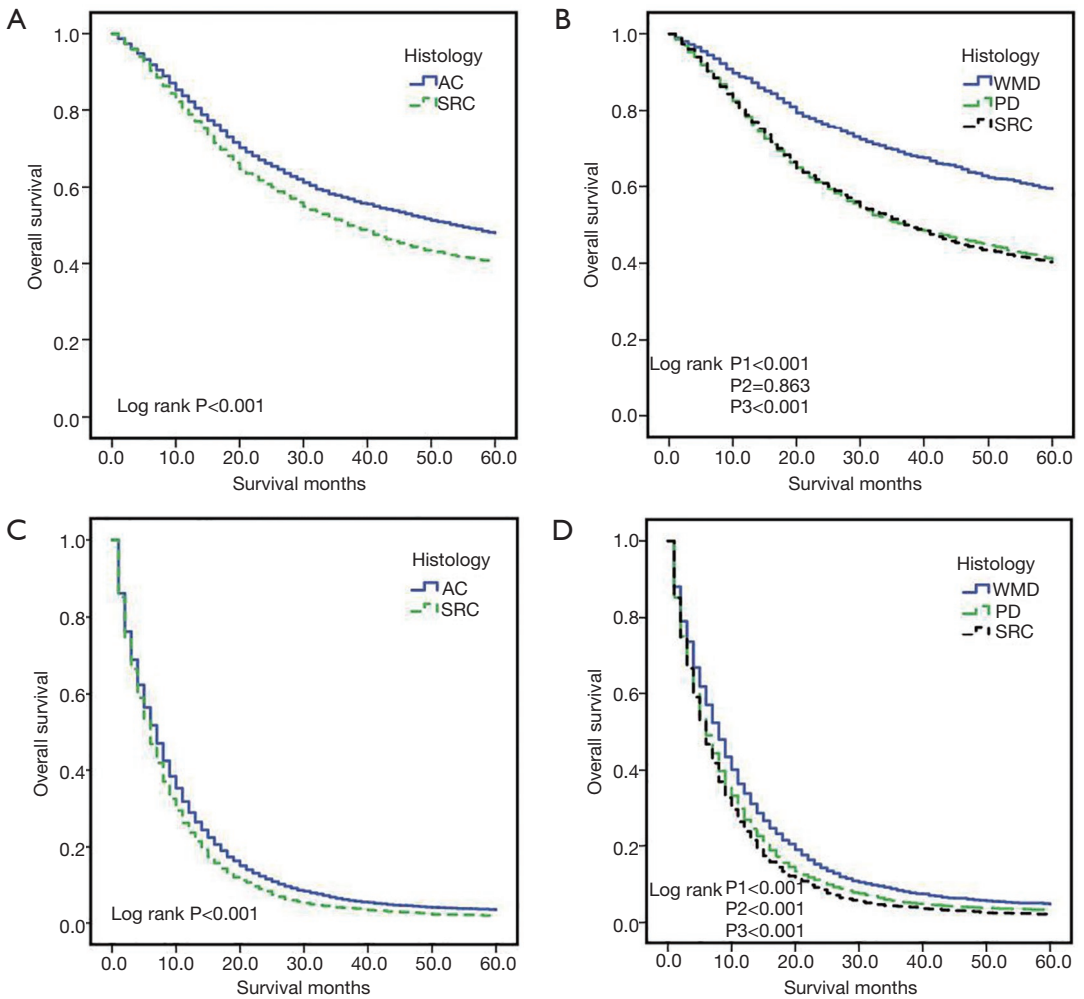

Figure 3 Kaplan-Meier (KM) survival curves for overall survival of (A) adenocarcinoma (AC) and signet ring cell carcinoma (SRC) in M0 group; (B) patients with well and moderately differentiated (WMD), and poorly differentiated (PD) AC and SRC in M0 group (C); AC and SRC in M1 group (D) patients with well and moderately differentiated (WMD), and poorly differentiated (PD) AC and SRC in M1 group. P1 for WMD and SRC, P2 for PD and SRC, P3 for WMD and PD.

WMD and PD (*Figure 3D*).

Predictors of mortality

Univariate analysis results are listed in *Table 3*. SRC was a prognostic risk factor (univariate Cox HR: 1.78; 95% CI: 1.62–1.96; P<0.001). Prognostic factors including age at diagnosis (≥70), race (white), advanced tumor stage, advanced node stage, tumor location, larger tumor size (≥5 cm) were correlated with increased mortality. Multivariable analysis results from the Cox regression model are shown in *Table 3*. SRC was an independent unfavorable predictor of survival (multivariable Cox HR: 1.47; 95% CI: 1.37–1.57; P<0.001). Age at diagnosis (multivariable Cox HR: 1.59; 95% CI: 1.48–1.70; P<0.001), white race, advanced tumor stage, advanced node stage, and larger tumor size (≥5 cm) were independently associated with mortality. Then, we further performed the univariable and multivariable analysis at each stage (*Figure 5*). The results showed that SRC, WMD, and PD had similar overall survival rates in stage I whereas both SRC and PD exhibited a worse OS than WMD in stage II and SRC had worse survival than WMD and PD in stage III. In the M1 group, multivariable analysis showed SRC; age ≥70; advanced node stage; no surgery; lymph node retrieved (<15); metastasis to bone, brain, liver and lung; tumor location; and absence of

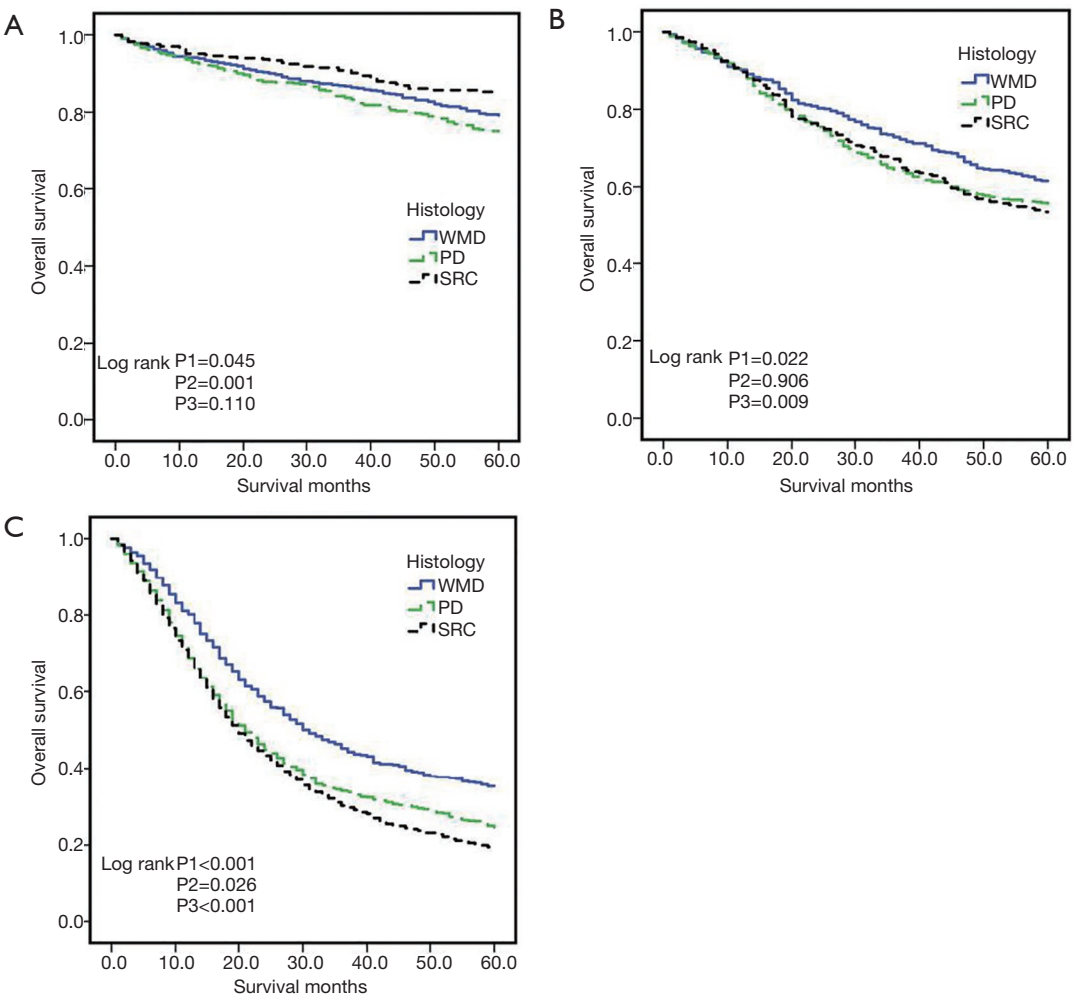

Figure 4 KM curves showing the overall survival of patients with well-to-moderately differentiated (WMD) and poorly differentiated (PD) and signet ring cell carcinoma (SRC) at: (A) stage I, (B) stage II, (C) stage III, AJCC 8th edition. P1 for WMD and SRC, P2 for PD and SRC, P3 for WMD and PD.

radiation therapy were independent prognostic factors of stage IV gastric cancer (*Table 4*); meanwhile, SRC revealed the worst survival. In general, SRC had a worse prognosis with disease progression.

Discussion

According to reports, the prevalence of SRC in the stomach ranges from 3.4–39% (9). In this study, 25.1% of the total patients had SRC. In respect of survival of SRC, Jiang *et al.* (7) reported that SRC was associated with a better survival rate in early gastric cancer while exhibiting a similar prognosis with AC in the advanced stage. Taghavi *et al.* (10) also suggested that there was no significant difference in the long-term survival between SRC and AC for advanced gastric cancer. However, there are considerable prognostic differences between Asian and American patients (11). The reasons are multifactorial, and SRC might have a different prognostic impact between Asian and American populations. Thus, the prognostic impact of SRC was only evaluated in American populations.

Meanwhile, due to the heterogeneity of gastric cancer, we further divided AC into WMD and PD. The results demonstrated that after adjustment for other prognostic factors, OS had no significant difference among SRC, PD, and WMD in stage I. With the progress of stages, the prognosis of SRC became gradually worse when compared to WMD and PD. Our study suggests that in American

Table 3 Univariate and multivariate analysis with overall survival of *M*0 group

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Histology				
WMD	1		1	
PD	1.77 (1.62–1.93)	<0.001	1.28 (1.21–1.35)	<0.001
SRC	1.78 (1.62–1.96)	<0.001	1.47 (1.37–1.57)	<0.001
SRC (*vs.* PD)	1.01 (0.93–1.09)	0.864		
Age (yrs)				
<70	1		1	
≥70	1.34 (1.25–1.43)	<0.001	1.59 (1.48–1.70)	<0.001
Gender				
Male	1			
Female	0.95 (0.89–1.02)	0.153		
Race				
White	1		1	
Black	1.03 (0.94–1.14)	0.531		
Other[a]	0.73 (0.67–0.79)	<0.001	0.78 (0.72–0.85)	<0.001
Tumor stage				
T1	1		1	
T2/T3/T4	4.15 (3.67–4.71)	<0.001	2.49 (2.19–2.85)	<0.001
Node stage				
Negative	1		1	
Positive	3.55 (3.26–3.87)	<0.001	2.64 (2.41–2.89)	<0.001
Tumor location				
Upper stomach	1		1	
Middle stomach	0.81 (0.71–0.92)	0.001	0.76 (0.67–0.87)	<0.001
Lower stomach	0.87 (0.80–0.95)	0.002	0.83 (0.76–0.91)	<0.001
Overlapping	1.30 (1.16–1.47)	<0.001	1.02 (0.90– 1.15)	0.808
Tumor size (cm)				
<5	1		1	
≥5	1.72 (1.60–1.85)	<0.001	1.19 (1.11–1.28)	<0.001
Radiation				
No	1			
Yes	1.02 (0.96–1.09)	0.555		

SRC, signet ring cell carcinoma; PD, poorly differentiated; WMD, well-to-moderately differentiated; HR, hazard ratio; CI, confidence interval; yrs, years; LN, lymph node. [a]includes: American Indian/AK Native, Asian/Pacific Islander.

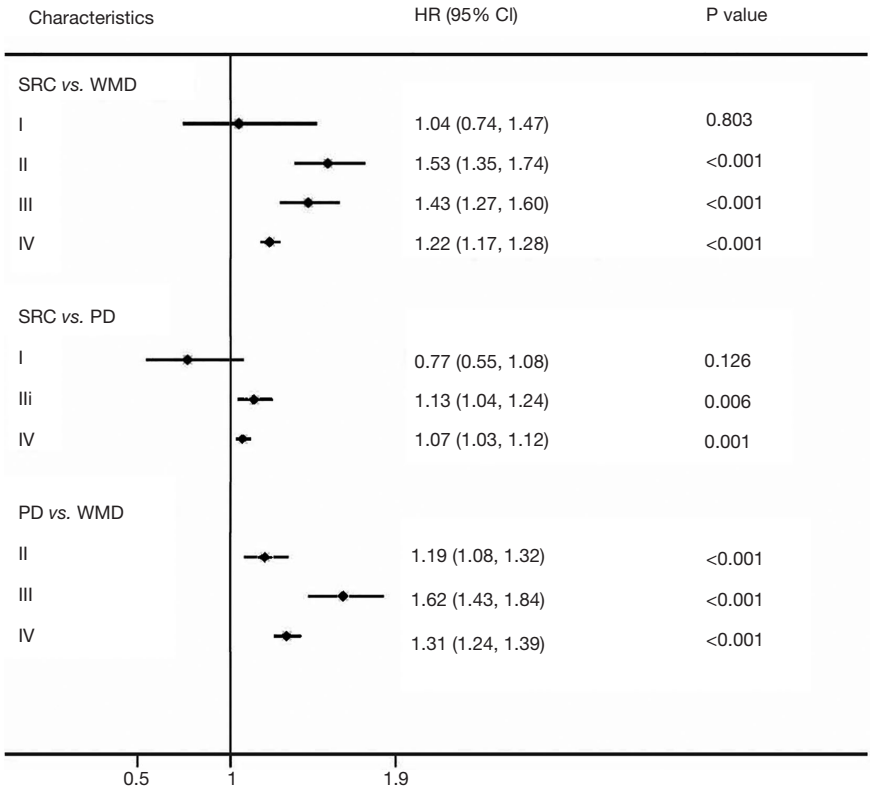

Figure 5 Multivariate analysis results of overall survival in well and moderately differentiated (WMD), and poorly differentiated (PD) adenocarcinoma and signet ring cell carcinoma (SRC) at each stage.

populations, SRC resembles hereditary diffuse gastric cancer (HDGC) in the characteristics and prognosis, which is inert in the mucosal layer at early stages and ultimately converts into aggressive phenotype in advanced GC (2). Thus, early aggressive screening and dissection can significantly improve SRC carcinoma patients' overall survival. Extensive therapy should be considered in advanced and metastatic gastric SRC.

Relatively high percentages of inadequate lymph node dissection were found in our study, including 47.2%, 56.3%, and 48.7% of patients with an examined LN <15 for the SRC, WMD, and PD in the M0 group, respectively. The study indicated that most American gastric cancer patients underwent D1 or D0 lymphadenectomy, which might lead to inadequate LN examination (12). Reid-Lombardo *et al.* found that the proportion of D1 lymphadenectomy was 56.7% in America (13). A National Cancer Data Base (NCDB) study (14) included 129,666 GC patients, and about 50% of them had more than 15 lymph nodes examined, which was similar to this study.

A higher rate of SRC type was diagnosed in younger patients and in female patients than AC type, which is consistent with previous studies (2,10,15). The mechanism that SRC gastric cancer accounts for a more significant proportion among young and female patients has not yet been explained. One theory is that sex hormones might influence the histological type. The staining pattern of ERβ in young patients is distinctive between signet ring cell carcinomas and other adenocarcinomas, implying that the pathogenesis of SRC differs from that of other cell types (16).

These two tumors also existed at different anatomical locations. Whereas signet ring cell carcinoma presented more in the body, lower stomach, and as an overlapping type, AC was more likely to present proximally. Numerous studies have reported that SRC type is more frequently observed with subserosa (T3) or serosa (T4), and is associated with a higher primary tumor metastasis to lymph node rate (15,17,18), which is consistent with our study. Moreover, the patients of SRC carcinoma with distant metastasis were more numerous than those of AC.

About one-third of patients with gastric cancer were

Table 4 Univariate and multivariate analysis with overall survival of M1 group

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Histology				
WMD	1		1	
PD	1.19 (1.17–1.25)	<0.001	1.22 (1.17–1.28)	<0.001
SRC	1.29 (1.22–1.35)	<0.001	1.31 (1.24–1.39)	<0.001
SRC (*vs.* PD)	1.08 (1.04–1.13)	<0.001	1.07 (1.03–1,12)	0.001
Age (yrs)				
<70	1		1	
≥70	1.19 (1.14–1.23)	<0.001	1.22 (1.17–1.27)	<0.001
Gender				
Male	1			
Female	1.01 (0.97–1.04)	0.791		
Race				
White	1			
Black	1.04 (0.97–1.11)	0.121		
Other[a]	0.73 (0.69–0.77)	0.134		
Tumor stage				
T1	1		1	
T2/T3/T4	0.91 (0.86–0.96)	<0.001	1.02 (0.97–1.08)	0.385
Node stage				
Negative	1		1	
Positive	1.50 (1.31–1.71)	<0.001	1.47 (1.25–1.72)	<0.001
Surgery				
No	1		1	
Yes	0.61 (0.58–0.64)	0.001	0.74 (0.68–0.81)	<0.001
LN retrieved				
<15	1		1	
≥15	0.83 (0.76–0.91)	0.001	0.85 (077–0.94)	0.001
Tumor location				
Upper stomach	1		1	
Middle stomach	1.08 (1.01–1.15)	0.028	0.72 (0.66–0.79)	<0.001
Lower stomach	1.01 (0.97–1.06)	0.758	0.78 (0.73–0.83)	0.202
Overlapping	1.17 (1.10–1.21)	<0.001	0.94 (0.86–1.03)	<0.001
Bone metastasis				
No	1		1	
Yes	1.40 (1.30–1.52)	<0.001	1.28 (1.16–1.41)	<0.001

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Brain metastasis				
No	1		1	
Yes	1.39 (1.16–1.67)	<0.001	1.44 (1.17–1.76)	<0.001
Liver metastasis				
No	1		1	
Yes	1.08 (1.02–1.14)	<0.001	1.10 (1.04–1.18)	0.003
Lung metastasis				
No	1		1	
Yes	1.31 (1.22–1.42)	<0.001	1.25 (1.12–1.39)	<0.001
Number of sites				
One	1		1	
Two	1.32 (1.21–1.45)	<0.001	1.03 (0.90–1.18)	0.654
Three	1.26 (1.03–1.55)	0.023	0.82 (0.63–1.07)	0.147
Four	2.20 (1.10–4.41)	0.026	0.99 (0.46–2.09)	0.969
Tumor size (cm)				
<5	1			
≥5	1.05 (0.99–1.11)	0.135		
Radiation				
No	1		1	
Yes	0.87 (0.83–0.91)	<0.001	0.92 (0.87–0.96)	0.001

SRC, signet ring cell carcinoma; PD, poorly differentiated; WMD, well-to-moderately differentiated; HR, hazard ratio; CI, confidence interval; yrs, years; LN, lymph node. [a]includes: American Indian/AK Native, Asian/Pacific Islander.

diagnosed with stage IV (19). A previous study indicated that liver metastasis was the most common site of hematogenous metastasis in GC (20), and bone metastasis was rare (21). However, we found that in SRC, bone metastasis accounted for nearly half of the patients with known metastasis sites. Also, the proportion of liver and lung metastasis were also relatively high for SRC patients. Therefore, it is necessary to carry out multi-type imaging techniques and multiple sites examination for SRC. Peritoneal metastasis was also more commonly found among gastric SRC carcinoma during surgery (17,22,23). Thus, studies demonstrated that a lower rate of curative resection was performed in the SRC histological type (22,24-26). The SEER database mainly included hematogenous metastasis, and there were no data about peritoneal metastasis. Thus, we could not compare the differences in peritoneal metastasis between SRC and AC.

Studies have shown that gene expression can also be different between SRC and adenocarcinoma in gastric cancer (27-29). The manifestations of signet ring cell carcinoma distinguished from AC might support gene expression results from a clinical standpoint. Molecular and genomic analysis of gastric cancer was conducted by The Cancer Genome Atlas Research Network (TCGA), and four subtypes were proposed (27). The analysis results may increase our comprehension of occurrence and development of gastric cancer and help to predict long-term survival more accurately in different cell types (27). It is also possible to make identifying molecular biomarkers that are specific to the SRC subtype (28,29) and the relative therapeutic targets. Finally, it helps us predict patients' sensitivity to chemotherapy (28) and select individualized treatment regimens.

Several limitations existed in our study. First, it was a retrospective study, and selection biases were thus inevitable. Second, the SEER database did not contain detailed information about surgical procedures and adjuvant treatment, which might have an impact on the prognosis. Third, there were no data about whether patients received preoperative therapy that might affect pathological stage. Fourth, detailed pathologic review was unclear in SEER database, pathologic diagnosis might be differed in different institutions.

In conclusion, SRC was significantly different from AC in clinicopathologic characteristics. Although the prognosis of SRC was similar to AC in the early stage, it had a poorer prognostic impact with the progression of the disease. Different therapeutic regimens and imaging evaluation should be applied according to histological types of gastric cancer.

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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.2019.09.06). 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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This article was approved by an independent ethical committee review board at Liaoning Cancer Hospital & Institute Ethical Committee (ID: 20181226). The individual informed consent was waived.

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Supplementary

Table S1 Clinicopathological characteristics of M1 group

Variables	Signet ring cell carcinoma (A) (N=4,059)		Well and moderately differentiated AC (B) (N=2,948)			Poorly differentiated AC (C) (N=6,362)		
	N	%	N	%	P (A *vs.* B)	N	%	P (A *vs.* C)
Age (yrs)					<0.001			<0.001
Mean	57		64			61		
SD	13.1		10.7			12.2		
Gender					<0.001			<0.001
Male	2,016	49.7	2,228	75.6		4,318	67.9	
Female	2,043	50.3	720	24.4		2,044	32.1	
Race					<0.001			0.621
White	2,941	72.7	2,137	72.6		4,596	72.4	
Black	490	12.1	478	16.2		807	12.7	
Other[a]	616	15.2	328	11.1		944	14.9	
T stage					<0.001			<0.001
T1	545	21.1	623	34.3		998	24.4	
T2	217	8.4	87	4.8		247	6.0	
T3	493	19.1	408	22.5		928	22.7	
T4a	445	17.2	215	11.8		669	16.3	
T4b	883	34.2	484	26.6		1,255	30.6	
Node stage					0.014			0.067
N0	20	6.9	15	10.7		37	7.9	
N1	17	5.8	15	10.7		45	9.6	
N2	52	17.9	33	23.6		70	14.9	
N3a	67	23.0	33	23.6		135	28.7	
N3b	135	46.4	38	27.1		184	39.1	
Surgery					<0.001			0.691
Yes	738	18.4	424	14.5		1,179	18.7	
No	3,280	81.6	2,503	85.5		5,133	81.3	
Examined LN					0.014			0.067
≥15	292	42.0	140	35.9		471	42.9	
<15[b]	389	58.0	250	64.1		618	57.1	
Tumor location					<0.001			0.878
Upper stomach	744	28.8	1,484	61.9		2,531	52.6	
Middle stomach	531	20.6	241	10.1		584	12.1	
Lower stomach	771	29.9	489	20.4		1,060	22.0	
Overlapping	533	20.7	184	7.7		636	13.2	
Tumor size (cm)					0.188			0.095
≥5	680	55.6	705	53.0		471	43.3	
<5	542	44.4	624	47.0		618	56.7	

yrs, years; SD, standard deviation; LN, lymph node. [a]includes American Indian/AK Native, Asian/Pacific Islander; [b]examined LN <15 was defined as pNx.