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The characteristics and prognostic value of signet ring cell histology in gastric cancer: A retrospective cohort study of 2199 consecutive patients

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Abstract

Although signet ring cell cancer (SRCC) has long been regarded as an adverse prognostic factor of gastric cancer, the findings of existing studies on this issue are inconsistent. We conducted a retrospective cohort study of 2199 consecutive patients with gastric cancer treated in a tertiary cancer hospital in Beijing, China, 1994 to 2013. The characteristics of SRCC and non-SRCC were compared. The prognostic effects of SRCC and other important clinicopathological factors on overall survival were evaluated by both univariate and multivariate Cox regression analyses and expressed as hazard ratio (HR) with 95% confidence interval (CI). SRCC accounted for 16.1% of gastric cancer, increasing from 6% to 20% over the last 2 decades, and was associated with younger age, female sex, poor differentiation, diffuse type, and distal location. SRCC (HR: 1.387, 95% CI: 1.177–1.634), stage (HR: 1.752, 95% CI: 1.458–2.106), surgery (palliative resection: HR: 0.712, 95% CI: 0.590–0.859; curative resection: HR: 0.490, 95% CI: 0.380–0.633), performance status (HR: 1.849, 95% CI: 1.553–2.201), and age (HR: 1.070, 95% CI: 1.001–1.143) were independent prognostic factors for gastric cancer, whereas time period of diagnosis, sex, and tumor location were not statistically significantly associated with overall survival. Subgroup analyses showed that the prognostic value of SRCC did not vary much with age, sex, performance status, stage, and surgery and chemotherapy status. As compared with non-SRCC, SRCC accounted for increasingly more of gastric cancer and was associated with younger age, female sex, poor differentiation, diffuse type, and distal location. It was an independent prognostic factor associated with worse survival in gastric cancer.

Abbreviations: CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, SRCC = signet ring cell cancer.

Keywords: cohort study, gastric cancer, prognosis, review, signet ring cell, survival

1. Introduction

Worldwide, gastric cancer is the fourth commonest cancer in terms of incidence and the third commonest cause of cancer-related deaths, with an estimated 952,000 new cases and 723,000 deaths every year.[1] Despite the advances in diagnosis and treatment options, the prognosis of gastric cancer has not been improved much over the last 2 decades,[2,3] with a 5-year survival rate of 25% to 30%.[4–6] Additionally, although the incidence of gastric cancer is decreasing, the proportion of signet ring cell cancer (SRCC) in gastric cancer was reported to be increasing in recent years.[7–10]

SRCC is a histologic diagnosis based on the microscopic characteristics of tumor, according to the World Health Organization classification.[11] It is defined by the presence of signet ring cell, which contains abundant intracytoplasmic mucin pushing nucleus to the periphery, in more than 50% of the tumor. The classifications by Lauren, Ming, and Sugano designate SRCC as "diffuse type," "infiltrative type," and "undifferentiated type," respectively.[12–14] Many studies have shown that the biological behavior of SRCC is distinct from that of other subtypes.[15] Due to its potential to infiltrate gastric wall and disseminate in the peritoneal cavity, SRCC has long been considered as an adverse prognostic factor of gastric cancer.[16,17]

However, the results of existing studies on the prognostic value of SRCC are inconsistent. For example, Shridhar et al[18] and Piessen et al[19] found that SRCC had shorter overall survival as compared with other patients (multivariate hazard ratio [HR]: 1.218, 95% confidence interval [CI]: 1.073–1.381 and 1.5, 95% CI: 1.1–2.0, respectively), while Kim et al[20] (multivariate HR: 0.948, 95% CI: 0.746–1.245) and Taghavi et al[17] (multivariate HR: 1.05, 95% CI: 0.96–1.11) found no differences in overall

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survival between SRCC and non-SRCC. Interestingly, some studies found that the independent prognostic value of SRCC may vary with the stage of cancer. For example, Jiang et al[21] found that among those with early gastric cancer SRCC was associated with significantly better survival as compared with non-SRCC (multivariate HR for non-SRCC vs SRCC: 2.366, 95% CI: 1.221–4.586), but it was not an independent predictive factor in patients with advanced disease (multivariate HR for non-SRCC vs SRCC: 1.171, 95% CI: 0.979–1.400).

China suffers from a heavy burden of gastric cancer, with the fourth highest incidence of gastric cancer among all countries.[22] Although some studies on the prognostic role of SRCC are available from China, most of them are limited by such problems as small sample size,[23,24] no multivariate analysis,[23] and being restricted to specific patient groups, for example, those who had undergone surgery.[21,24–26] We therefore recruited a large sample of patients to further investigate the prognostic value of SRCC in gastric cancer through a multivariate approach, adjusting for a number of important clinicopathological characteristics, with subgroup analyses according to age, gender, performance status, stage, surgery and chemotherapy. We aimed to examine the independent prognostic value of SRCC in relation to those of other variables. We also wanted to know if its prognostic value, if any, would vary with the status of selected clinicopathological factors.

2. Methods

2.1. Patients and data collection

Two thousand one hundred ninety-nine consecutive patients diagnosed with gastric cancer admitted to the Department of GI Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China during January 1994 to July 2013 were included in the present study. From their medical records the data on date of diagnosis, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, tumor location at diagnosis, stage of cancer, histological type (SRCC or non-SRCC), differentiation, Lauren classification, surgical procedure, neoadjuvant therapy (if applicable), chemotherapy regimens (if any), and the outcome of our interest, that is, overall survival, were extracted anonymously.

For convenience of analysis, date of diagnosis was categorized into 4 groups: 1994 to 1998, 1999 to 2003, 2004 to 2008, and 2009 to 2013. Age was also divided into 4 groups: <40, 40 to 49, 50 to 59, and ≥60 years. ECOG performance status is recommended by the World Health Organization to measure patients' functional performance, whose score ranges from 0 to 5, with 0 representing the best status.[27] In this study, ECOG performance status was divided into 2 groups, that is, 0 to 1 and ≥2, for analysis. Tumor location at diagnosis included fundus, esophagogastric junction, body, antrum, and multisite. The 7th edition of the American Joint Committee on Cancer staging system was employed to describe the pathological stage of cancer.[28]

The World Health Organization classification of histological types was used to define SRCC. This criterion has not been changed through the whole study and all tissues were examined by experienced pathologists. Lauren classification included intestinal, diffuse, and mixed types. As it was not routinely used in Peking University Cancer Hospital until recently, Lauren classification was available for only a small part of the patients included for this study. Surgical procedure included curative resection (radical operation) and palliative operation, and neoadjuvant therapy was used only for the patients who received radical operation. First-line chemotherapy regimens, if any, were divided into regimen consisting of 1 to 2 drugs and that with more than 2 drugs. Also, the type of drugs was recorded, such as platinum based, taxane based, both, and others. Whether second-line chemotherapy was given to patients was also recorded. Overall survival was defined as the time from diagnosis to all-cause death or the last date of follow-up, whichever earlier. Informed consent was obtained from each patient at the time of admission to hospital. The study was approved by the Ethics Committee of Peking University Cancer Hospital.

2.2. Statistical analysis

Patient characteristics were compared between SRCC and non-SRCC groups using Chi-square test. Overall survival rates were computed and survival curves generated by using the Kaplan–Meier method. Both univariate and multivariate analyses were conducted to evaluate the prognostic value of each clinicopathological factor mentioned above. Log-rank test was adopted to detect the difference between survival curves. Cox regression model including all clinically relevant variables as listed above was used to do multivariate analyses to control the potential confounding. The prognostic effects of patient characteristics on overall survival were expressed with HR and 95% CI. Sensitivity analyses were conducted to test the robustness of main results when only the carcinomas containing 100% signet ring cells were counted as SRCC.[29] Subgroup analyses according to age, sex, ECOG performance status, stage of cancer, surgery and chemotherapy status to see if the prognostic effect of SRCC, if any, would change with these important clinical factors. The level of statistical significance was set at $\alpha = 0.05$, except for the test for subgroup difference, for which the level was $\alpha = 0.10$. All analyses were conducted using the IBM SPSS Statistics 22.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. Of the 2199 patients included for analysis, 354 (16.1%) had SRCC and 1845 (83.9%) had non-SRCC. The proportion of SRCC in gastric cancer increased steadily from 6.0% in the period of 1994 to 1998 to 20.0% in the period of 2009 to 2013 ($P < 0.001$). SRCC was more frequently seen in younger patients than in older ones, with a proportion of 32.3% in those aged <40 years decreasing to 10.5% in those aged ≥60 years ($P < 0.001$). Female were more likely to have SRCC than male (26.6% vs 12.2%, $P < 0.001$). The male-to-female ratio in SRCC was 1.24, as compared to the ratio of 3.24 in non-SRCC. Carcinomas located in the fundus or esophagogastric junction part of stomach were less likely to be SRCC than those in other sites ($P < 0.001$). Although Lauren classification was available for only 255 patients, statistically significance was observed between different types, with SRCC much more commonly seen in diffuse (47.7%) and mixed types (21.1%) than in intestinal type (3.4%) ($P < 0.001$). The majority of SRCC were poorly differentiated. Stage I cancer appeared to have less SRCC, but the difference between stages was not statistically significant. The distribution of SRCC did not vary considerably in the subgroups defined by ECOG performance status and surgery status. Among the patients who received radical operation, 4.2% (42/995) received neoadjuvant therapy, and there were more SRCC (28.6%) in the group with

Table 1

Patient characteristics.

Factors	No. of patients (% of row)			*P* for χ^2 test
	Total no. of rows	SRCC (N = 354, 16.1%)	Non-SRCC (N = 1845, 83.9%)	
1. Time period of diagnosis (n = 2199)				<0.001
1994–1998	200	12 (6.0)	188 (94.0)	
1999–2003	364	39 (10.7)	325 (89.3)	
2004–2008	736	123 (16.7)	613 (83.3)	
2009–2013	899	180 (20.0)	719 (80.0)	
2. Age (n = 2186)				<0.001
<40	235	76 (32.3)	159 (67.7)	
40–49	372	82 (22.0)	290 (78.0)	
50–59	591	90 (15.2)	501 (84.8)	
≥60	988	104 (10.5)	884 (89.5)	
3. Sex (n = 2198)				<0.001
Female	593	158 (26.6)	435 (73.4)	
Male	1605	196 (12.2)	1409 (87.8)	
4. ECOG (n = 1974)				0.48
0–1	1673	267 (16.0)	1406 (84.0)	
≥2	301	53 (17.6)	248 (82.4)	
5. Tumor location (n = 2108)				<0.001
Fundus	668	66 (9.9)	602 (90.1)	
EGJ	54	5 (9.3)	49 (90.7)	
Body	560	128 (22.9)	432 (77.1)	
Antrum	581	96 (16.5)	485 (83.5)	
Multisite	245	51 (20.8)	194 (79.2)	
6. Stage (n = 2076)				0.100
I	77	8 (10.4)	69 (89.6)	
II	173	34 (19.7)	139 (80.3)	
III	724	104 (14.4)	620 (85.6)	
IV	1102	191 (17.3)	911 (82.7)	
7. Differentiation (n = 1833)				<0.001
Well differentiated	47	0 (0.0)	47 (100.0)	
Well–moderately differentiated	47	0 (0.0)	47 (100.0)	
Moderately differentiated	390	6 (1.5)	384 (98.5)	
Moderately–poorly differentiated	363	12 (3.3)	351 (96.7)	
Poorly differentiated	984	166 (16.9)	818 (83.1)	
Undifferentiated	2	0 (0.0)	2 (100.0)	
8. Lauren type (n = 255)				<0.001
Intestinal	89	3 (3.4)	86 (96.6)	
Diffuse	128	61 (47.7)	67 (52.3)	
Mixed	38	8 (21.1)	30 (78.9)	
9. Surgical procedure (n = 2167)				0.20
No	834	146 (17.5)	688 (82.5)	
Palliative operation	323	53 (16.4)	270 (83.6)	
Radical operation	996	151 (15.2)	845 (84.8)	
10. Neoadjuvant therapy (n = 995)				0.013
No	953	139 (14.6)	814 (85.4)	
Yes	42	12 (28.6)	30 (71.4)	
11. 1st-line chemotherapy (n = 2161)				<0.001
0 drug (no chemotherapy)	446	68 (15.2)	379 (84.8)	
1–2 drugs	971	193 (19.9)	778 (80.1)	
>2 drugs	744	89 (12.0)	655 (88.0)	
Among those who received chemotherapy:				
(1) Regimen of 1st-line chemotherapy (n = 1716)				<0.001
Platinum based	696	86 (12.4)	610 (87.6)	
Taxane based	480	122 (25.4)	358 (74.6)	
Platinum + taxane based	335	55 (16.4)	280 (83.6)	
Other	205	19 (9.3)	186 (90.7)	
(2) 2nd-line chemotherapy (n = 1714)				0.27
No	1186	186 (15.7)	1000 (84.3)	
Yes	528	94 (17.8)	434 (82.2)	

ECOG = Eastern Cooperative Oncology Group, EGJ = esophagogastric junction, SRCC = signet ring cell cancer.

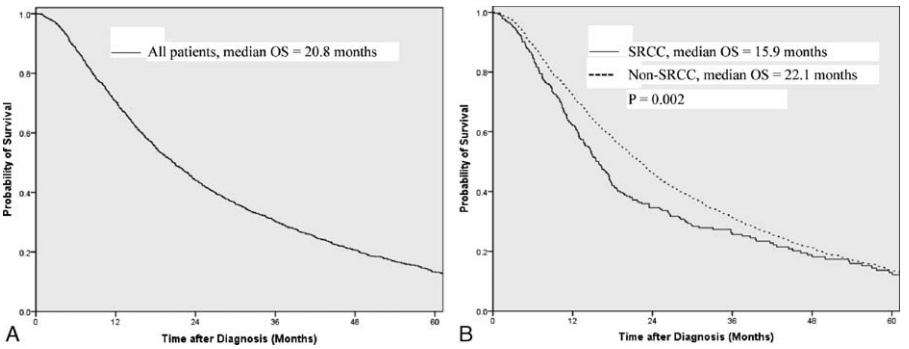

Figure 1. Survival curves for (A) all patients; (B) SRCC vs non-SRCC.

neoadjuvant therapy than in the one without (14.6%) (P= 0.013). Regarding palliative chemotherapy, there were more SRCC in the group receiving 1 to 2 drugs than in those receiving none or more than 2 drugs, and the taxane-based treatment group had more SRCC than other groups.

3.2. Overall survival and prognostic factors

Kaplan–Meier survival curves are shown in Fig. 1. Of the 2199 cases, 1274 (57.9%) died during follow-up. The median overall survival of all patients as a whole was 20.8 (95% CI: 19.5–22.1) months (Fig. 1A). For SRCC and non-SRCC, the median overall survival was 15.9 (95% CI: 14.1–17.8) and 22.1 (95% CI: 20.7–23.5) months, respectively (Fig. 1B, log-rank test: P= 0.002). The results of univariate and multivariate Cox regression analyses to evaluate the prognostic value of various factors are shown in Table 2. Multivariate analyses showed that SRCC was an independent prognostic factor associated with worse survival (HR: 1.387, 95% CI: 1.177–1.634). Sensitivity analyses by changing the definition of SRCC (only the carcinomas containing 100% SRCC cells were counted as SRCC) did not change the results much (HR: 1.377, 95% CI: 1.081–1.754). We did not include differentiation in the multivariate analyses, as the majority of SRCC were poorly differentiated and thus inclusion of differentiation into the model would cause multicollinearity problem, in which case the prognostic effect of SRCC could be masked by differentiation. Lauren classification was not included in multivariate analyses either, because it was available for only a few patients and its inclusion in the model would severely reduced the statistical power.

Apart from SRCC, older age at diagnosis (HR: 1.070, 95% CI: 1.001–1.143), poorer ECOG performance status (HR: 1.849, 95% CI: 1.553–2.201), and more advanced stage (HR: 1.752, 95% CI: 1.458–2.106) were also independent prognostic factors associated with worse overall survival, whereas surgery, including palliative resection (HR: 0.712, 95% CI: 0.590–0.859) and curative resection (HR: 0.490, 95% CI: 0.380–0.633), was independent prognostic factor associated with better overall survival. In this cohort, no evidence was found that the time period of diagnosis, sex, tumor location, neoadjuvant therapy, and first-line chemotherapy, regardless of the number and types of drugs used, had prognostic value, while second-line chemotherapy (HR: 0.777, 95% CI: 0.666–0.907) was associated with better survival. Subgroup analyses (Table 3) showed that the prognostic value of SRCC did not vary with sex, performance status, stage, and surgery and chemotherapy status.

4. Discussion

Although SRCC has long been regarded as an adverse prognostic factor of gastric cancer, the findings of existing studies on this issue are inconsistent (see Appendix 1 in the "Supplementary Appendix 1.docx," http://links.lww.com/MD/B94). Here we tried to compare the characteristics of SRCC with those of non-SRCC, examine its prognostic value with control fro confounding, compare it with other major prognostic factors, and also take into account the potential interaction of SRCC with important clinicopathological factors in a single study.

SRCC was found to account for 16.1% of all patients with gastric cancer, falling in the range reported by previous studies.[30,31] Over the last 2 decades, the proportion of SRCC increased from 6% to 20%, which was consistent with the findings of previous studies from Western countries like France and the United States.[8–10,32] Of note, this trend of proportion does not necessarily mean that SRCC was increasing in incidence, because the overall incidence of gastric cancer has been decreasing. For example, the U.S. national surveillance data showed that the incidence of intestinal type decreased consistently from 1978 to 2005, whereas the incidence of diffuse type, which is significantly associated with SRCC, increased through 2000 but then declined in recent years.[33] In this study, SRCC, as compared with non-SRCC, was found to be more frequent in younger patients, female, diffuse type, and other sites than the fundus of stomach, such as the middle and lower thirds of stomach. These findings are in line with previous studies from China, other Asian countries, as well as Western countries.[17,34,35] The association of SRCC with stage of gastric cancer has been controversial. Some studies found that SRCC was more frequent in early stage gastric cancer, which might be due to its depressed lesions and characteristic appearance that make it easily detected,[36] while others found more SRCC in advanced gastric cancer, arguing that it was because most SRCC were located in gastric corpus, which led to the late onset of clinical symptoms.[31] In the present study, SRCC appeared to be slightly more in advanced stage, but the difference was not statistically significant. Thus, this issue remains to be further investigated.

A lot of studies have evaluated the prognostic value of various factors in gastric cancer. Two studies from the United States[17,37] found that Asian people had better prognosis than African American, whereas white people and Hispanic people lay in between them with comparable risk of mortality. Gill et al[38] found that the benefit from surgery was greater in Asians than

Table 2

The prognostic value of patient characteristics.

Factors	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
1. Time period of diagnosis				
1994–1998	1		1	
Every one-level increment*	1.128 (1.059–1.202)	<0.001	1.058 (0.978–1.144)	0.161
2. Age				
<40	1		1	
Every one-level increment*	1.052 (0.996–1.112)	0.071	1.070 (1.001–1.143)	0.045
3. Sex				
Female	1		1	
Male	0.893 (0.791–1.010)	0.071	0.925 (0.798–1.072)	0.302
4. ECOG				
0–1	1		1	
≥2	1.911 (1.626–2.245)	<0.001	1.849 (1.553–2.201)	<0.001
5. Tumor location				
Fundus	1		1	
EGJ	0.786 (0.506–1.219)	0.282	0.713 (0.446–1.141)	0.158
Body	1.027 (0.886–1.192)	0.720	1.053 (0.884–1.254)	0.563
Antrum	0.949 (0.820–1.098)	0.485	1.129 (0.956–1.334)	0.154
Multisite	1.288 (1.074–1.544)	0.006	1.146 (0.934–1.407)	0.191
6. Stage				
I	1		1	
Every one-level increment*	2.671 (2.414–2.956)	<0.001	1.752 (1.458–2.106)	<0.001
7. Histology				
Non-SRCC	1		1	
SRCC	1.246 (1.081–1.436)	0.002	1.387 (1.177–1.634)	<0.001
8. Lauren type				
Intestinal	1		—	
Diffuse	1.362 (1.004–1.848)	0.047	—	—
Mixed	0.926 (0.598–1.433)	0.729	—	—
8. Surgical procedure				
No	1		1	
Palliative operation	0.623 (0.530–0.731)	<0.001	0.712 (0.590–0.859)	<0.001
Radical operation	0.241 (0.212–0.274)	<0.001	0.490 (0.380–0.633)	<0.001
10. Neoadjuvant therapy				
No	1		1	
Yes	1.183 (0.807–1.736)	0.388	0.901 (0.555–1.461)	0.673
11. 1st-line chemotherapy				
0 drug (no chemotherapy)	1		1	
1–2 drugs	1.824 (1.481–2.246)	<0.001	1.039 (0.809–1.335)	0.763
>2 drugs	2.150 (1.735–2.665)	<0.001	1.222 (0.940–1.589)	0.134
Among those who received chemotherapy:				
(1) Regimen of 1st-line therapy				
Platinum based	1		1	
Taxane based	0.929 (0.808–1.068)	0.300	1.052 (0.890–1.244)	0.552
Platinum + taxane based	0.970 (0.833–1.131)	0.698	0.970 (0.798–1.178)	0.756
Other	0.810 (0.647–1.012)	0.064	0.959 (0.668–1.104)	0.235
(2) 2nd-line therapy				
No	1		1	
Yes	0.817 (0.725–0.921)	0.001	0.777 (0.666–0.907)	0.01

* For details of the levels of factors, please refer to Table 1.

ECOG = Eastern Cooperative Oncology Group, EGJ = esophagogastric junction, SRCC = signet ring cell cancer.

non-Asians. Older age was consistently found to be associated with worse prognosis in previous studies,[8,17,34,37,39,40] which was replicated in the present one. However, as the way age was treated in regression models differed across studies (e.g., age as a continuous or ordinal variable), the results from different studies are not directly comparable. To our knowledge, no studies have found significant association between sex and overall survival of gastric cancer in multivariate analysis, although Dittmar et al[41] found that female had shorter recurrence-free survival than male. In this study, we found no evidence for the prognostic value of sex either. There was no statistically significant association between time period of diagnosis and overall survival, indicating that the prognosis of gastric cancer has not been improved much over the last 2 decades, similar to the situation in Western countries.[2,3] Not surprisingly, stage at diagnosis, surgery (especially curative resection) and ECOG performance status were found to be the 3 most powerful prognostic factors for gastric cancer, while the impact of age at diagnosis was modest. We did not find that tumor location was associated with overall survival, contrary to previous studies showing that proximally located cancer had worse prognosis than those located in antrum or pylorus.[37,38,42]

As mentioned previously in the Introduction section, the prognostic value of SRCC has long been controversial, with its relation to the stage of cancer being especially heavily

Table 3

Subgroup analyses for the prognostic value of SRCC.

Subgroups	Median survival (mo) of SRCC vs non-SRCC	Multivariate HR (95% CI)	*P* for difference across strata
1. Age			
<40	13.6 vs 23.5	1.758 (1.121–2.756)	0.27
≥40	15.9 vs 21.8	1.339 (1.119–1.604)	
2. Sex			
Female	17.0 vs 20.2	1.281 (0.966–1.698)	0.53
Male	15.0 vs 22.5	1.431 (1.163–1.765)	
3. ECOG			
0–1	16.7 vs 23.2	1.412 (1.179–1.690)	0.47
≥2	8.7 vs 13.1	1.181 (0.755–1.849)	
4. Stage			
I–III	37.5 vs 37.7	1.296 (0.973–1.725)	0.73
IV	10.4 vs 12.9	1.378 (1.123–1.691)	
5. Surgical procedure			
No	9.5 vs 12.1	1.338 (1.060–1.688)	0.55
Palliative	13.0 vs 17.8	1.766 (1.129–2.763)	
Radical	39.5 vs 39.1	1.373 (1.028–1.834)	
6. Chemotherapy			
No	38.7 vs 36.2	1.720 (0.935–3.165)	0.44
Yes	14.7 vs 20.8	1.341 (1.131–1.591)	

ECOG = Eastern Cooperative Oncology Group, SRCC = signet ring cell cancer.

investigated. Difference in statistical methods might partly explain the heterogeneity of results from existing studies. For example, some studies conducted univariate analyses only, while others employed a multivariate approach. Studies doing both kinds of analysis have shown that the statistically significant association observed in univariate analyses could disappear in multivariate analyses after control for confounding.[20,43] However, even the results of multivariate analyses from different studies still contradicted with each other in some cases. Several hypotheses have been proposed to explain the difference.[15,44] In this study, SRCC was found to be significantly associated with worse survival in gastric cancer, which did not vary with age, sex, ECOG performance status, stage of cancer, and surgery and chemotherapy status. This may be because SRCC has greater potential for infiltrative growth, lymph node metastasis, and distant metastasis characterized by peritoneal dissemination, which are all associated with poor prognosis.[19,45] Our findings support the notion that SRCC may represents a disease biologically distinct from gastric adenocarcinoma.[46] In fact, some gene expression data also supported this concept.[47] Thus, the results of this study have important implications for the clinical management of SRCC, including the type of surgery to be conducted, use of adjuvant therapy and follow-up strategy.

Randomized controlled trials and meta-analyses showed that chemotherapy was effective and could prolong the overall survival by approximately 6 months as compared with best supportive alone in patients with advanced gastric cancer.[48] Interestingly, first-line chemotherapy was not associated with better survival in the present study. The 3-drug regimens even seemed to have statistically nonsignificant detrimental effects. It is not impossible that these results were confounded by stage and surgery; however, we have actually adjusted for these factors in the multivariate analyses. In addition, our post hoc stratified analyses showed that the results did not differ much between the patients receiving surgery and those who did not. Thus, it is unlikely that the results have been distorted by the surgery status of patients. We propose that the difference between our results and those of randomized trials favoring chemotherapy could be due to the following reasons among others. First, overall survival in randomized trials usually starts from the time of randomization, while in this study it starts from the time of first diagnosis of gastric cancer. The former approach excludes the survival time from first diagnosis to randomization, and could not reflect the prognostic impact of chemotherapy relative to that of other factors such as surgery. Second, patients included in randomized trials are generally in better condition, more homogeneous, and more likely to respond to chemotherapy than those treated in routine clinical settings where the efficacy of chemotherapy is greatly diluted by various factors. Third, the present study is a retrospective one and may suffer from unmeasurable bias. For example, there might be some important confounding factors that were not adjusted for by multivariate analyses.

Apart from the retrospective nature of study as just mentioned, another limitation of this study is that we obtained limited data on Lauren classification and no data on tumor size, lymphovascular invasion, lymph node metastasis, distant metastasis and time to recurrence, which are important to describe the behaviors of tumor and could help better explain the adverse prognostic effect of SRCC. Despite these problems, we think this study still has its own merit due to the relatively large sample size, comprehensive data analyses, and systematic summary of literature. In the future, specific strategies most suitable for the treatment and management of SRCC may be worthy of further investigation.

In conclusion, we found that SRCC, as compared with non-SRCC, accounted for increasingly more of gastric cancer and was associated with younger age, female sex, poor differentiation, diffuse type, and distal location. It was an independent prognostic factor associated with worse survival in gastric cancer. Early detection and aggressive treatments for the disease are thus warranted.

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