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Clinical Efficacy of Radiotherapy Combined with Surgery for Locally Advanced Gastric Signet-Ring-Cell Carcinoma

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Abstract

The Incidence of Gastric Signet-Ring-Cell Carcinoma (GSRCC) is increasing yearly. However, the effectiveness of strategies for treatment of GSRCC patients remains ambiguous. This study was aimed to assess the clinical efficacy of radiotherapy combined with surgery for locally advanced Gastric Signet-Ring-Cell Carcinoma (GSRCC). Clinical data of patients with locally advanced GSRCC diagnosed by postoperative pathology from 2000 to 2016 were collected from the US Surveillance, Epidemiology and End Results (SEER) database. All the enrolled patients were divided into three groups according to treatment type: Surgery alone (S; N=727), surgery with preoperative radiotherapy (RT+S; N=138), surgery with postoperative radiotherapy (S+RT; N=548). It was found that the median Overall Survival (OS) time in S, RT+S and S+RT group was 19, 26 and 33 months, respectively; the Overall Survival (OS) rate was 19.5%, 26.9% and 34.0%, respectively; the median Cancer-Specific Survival (CSS) time was 29, 31 and 43 months, respectively; and the CSS rate was 32.4%, 35.3% and 43.6%, respectively. After performing Propensity Score Matching (PSM), it was found that the OS rate was significantly lower in S group than in RT+S or S+RT group (all $P<0.05$) and the CSS rate was lower in the S group than in the S+RT group ($P<0.0001$) while there was no significant difference between S and RT+S groups. The OS and CSS were not significantly different between RT+S and S+RT groups. Cox multivariate analysis showed that radiotherapy was an independent prognostic factor for OS and CSS of locally advanced GSRCC. Taken together, compared to surgery alone, surgery combined with preoperative or postoperative radiotherapy is beneficial to the long-term survival of patients with locally advanced GSRCC.

Keywords: Gastric signet-ring-cell carcinoma; Radiotherapy; Surgical therapy; Clinical efficacy

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Introduction

Gastric Cancer (GC) is one of the most frequently occurring digestive tract cancers and ranks the fifth among malignant tumors and the fourth in the cancer-related deaths [1]. There are several grading systems for GC based on the morphological structures, biological behaviors and molecular mechanisms. At present, there are three main classification systems for GC which are Bormann classification, Lauren classification and World Health Organization (WHO) classification. Signet-Ring-Cell Carcinoma (SRCC) is one of the WHO classifications, microscopically characteristic of a large amount of mucus in the cancer cells that pushes the nucleus to the side of the cell. The whole cell is signet ring-like and its malignancy is higher than that of extracellular mucus [2].

In recent years, epidemiological investigations have shown that the incidence of Gastric Signet-Ring-Cell Carcinoma (GSRCC) is increasing yearly [3]. Because of the lack of typical clinical symptoms and suitable disease biomarkers, pathological mechanisms and precancerous lesions are unclarified [4]. Besides, the early diagnosis rate remains low and most patients are first diagnosed in advanced stages [5,6]. Previous studies have shown that compared to non-GSRCC, advanced GSRCCs are more aggressive, with a higher rate of lymph node metastasis and peritoneal implantation [7] being the most common cause of recurrence. Radiotherapy, add-on therapy to surgery, has been successfully used in the treatment of colorectal cancer, breast cancer, esophageal cancer and other malignant tumors with a high recurrence rate. Currently, much attention has been focused on the role of radiotherapy in the treatment of GC.

However, the effectiveness for patients with GSRCC remains disputed [8,9]. This study aimed to evaluate the efficacy of surgery combined with radiotherapy for locally advanced GSRCC using population-based data from the Surveillance, Epidemiology and End Results (SEER) program.

Materials and Methods

Study population

All data of enrolled patients were extracted from the SEER database (https://seer.cancer.gov/) using the SEER*stat software (version 8.3.8). The postoperative pathologic stage was classified based on the American Joint Committee on Cancer (AJCC) staging, seventh edition. The inclusion criteria were as follows: 1) Patients diagnosed between January 1st, 2000 and December 31st, 2016; 2) Patients who underwent radical surgery; 3) the pathological diagnoses of GSRCC were confirmed postoperatively; 4) Patients were pathologically at stages II and III after surgery. The exclusion criteria were as follows: 1) Patients with local excision, tumors or lymph nodes biopsy and combined organ resection; 2) Patients with stage I or IV; 3) Cases with missing information.

Of note, the SEER database is an open-access cancer database that contains no identifier and is publicly available. Therefore, this study was exempt from the approval by the Institutional Review Board of the First Affiliated Hospital of Fujian Medical University, and the informed consent was waived.

Data collection

The data collected included: 1) Demographic characteristics including age, gender and race; 2) Pathological characteristics including tumor location, tumor size, depth of infiltration, TNM staging and differentiation grade; 3) Treatment sequences; 4) Follow-up information including outcome, cause of death and survival time. Overall Survival (OS) and Cancer-Specific Survival (CSS) were used as prognostic indicators. OS was defined as the duration from the initial diagnosis to any causes of death. CSS was defined as the duration from the initial diagnosis to cancer-related death.

Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test. Univariate and multivariate Cox proportional hazard regression models were constructed to explore the associations between clinicopathological characteristics and OS, as well as CSS. All parameters that were statistically significant in the univariate analysis were included in the multivariate Cox model. OS and CSS were estimated using the Kaplan-Meier method and differences in survival were examined using the log-rank test.

Propensity Score Matching (PSM) was used to reduce confounding factors. The matching process was conducted with a minimum-distance scoring method and patients with the nearest propensity scores were matched between two groups using a 1:1 scheme. Matching variables included gender, race, age, tumor location, tumor size, depth of infiltration, TNM staging and differentiation grade. The caliper width allowed was 0.05. Patients without matched observation were excluded. A p-value <0.05 was considered statistically significant. PSM was carried out using the "Match It" package in statistical software R version 3.6.1 (The R Foundation. Vienna, Austria). All other analyses were performed using IBM SPSS version 21.0 (IBM SPSS, Armonk, NY).

Results

Clinical and pathological characteristics

A total of 1,413 locally advanced GSRCC patients were included. Patients were divided into three groups based on treatment type: Surgery alone (S) group, preoperative radiotherapy + surgery (RT+S) group, and surgery + postoperative radiotherapy (S+RT) group.

Table 1: Patient and tumor characteristics compared by treatment type.

Characteristics	S	RT+S	S+RT	$\chi2$	P
	N=727	N=138	N=548		
Race				36.378	<0.0001
White	499 (68.6)	125 (90.6)	353 (64.4)		
Black	90 (12.4)	8 (5.8)	78 (14.2)		
Others	138 (53.1)	5 (3.6)	117 (21.4)		
Gender				28.525	<0.0001
Male	393 (54.1)	107 (77.5)	293 (53.5)		
Female	334 (45.9)	31 (22.5)	255 (46.5)		
Age (years)				108.5	<0.0001
≤50	125 (17.2)	23 (16.7)	145 (26.5)		
51~ ≤ 65	197 (27.1)	57 (41.3)	220 (40.1)		
66~ ≤ 75	199 (27.4)	48 (34.8)	132 (24.1)		
>75	206 (28.3)	10 (7.2)	51 (9.3)		
Tumor Site				281.51	<0.0001
Cardia/fundus	190 (26.1)	129 (93.5)	120 (21.9)		
body	139 (19.1)	2 (1.4)	101 (18.4)		
Antrum/pylorus	398 (54.7)	7 (5.1)	327 (59.7)		
Tumor grade				0.762	0.683
Moderately/highly	15 (2.1)	4 (2.9)	15 (2.1)		
Poorly	712 (97.9)	134 (97.1)	533 (97.3)		
TNM stage				2.395	0.302
II	303 (41.7)	60 (43.5)	208 (38.0)		
III	424 (58.3)	78 (56.5)	340 (62.0)		
Depth of infiltration				33.711	<0.0001
T1	19 (2.6)	3 (2.2)	17 (3.1)		
T2	214 (29.4)	43 (31.2)	189 (34.5)		
T3	324 (44.6)	86 (62.3)	232 (42.3)		
T4	170 (23.4)	6 (4.3)	110 (20.1)		
Tumor size (mm)				4.111	0.662
≤ 20	79 (10.9)	20 (14.5)	57 (11.0)		
21~ ≤ 40	227 (31.2)	49 (35.5)	172 (31.4)		
41~ ≤ 60	198 (27.2)	30 (21.7)	147 (26.8)		
>60	223 (30.7)	39 (28.3)	172 (31.4)		

There were 727 cases in the S group, 138 cases in the RT+S group and 548 cases in the S+RT group. A comparison of the clinicopathological characteristics according to treatment group is detailed in Table 1. Gender, race, age, tumor location and depth of infiltration showed significant differences among the three groups whereas there were no significant differences in TNM staging, differentiation grade and tumor size.

Outcomes before PSM

The median overall survival time in the S, RT+S and S+RT groups was 19, 26 and 33 months, respectively. The OS rate in the S group (19.5%) was significantly lower than that in the RT+S (26.9%) or the S+RT (34.0%) group (p<0.05). There was no significant difference in the OS between the RT+S group and the S+RT group (Figure 1A). The median CSS time in the S, RT+S and S+RT groups was 29, 31 and 43 months, respectively. The CSS rate in the S group (32.4%) was significantly lower than that in the S+RT group (43.6%) (p<0.05)

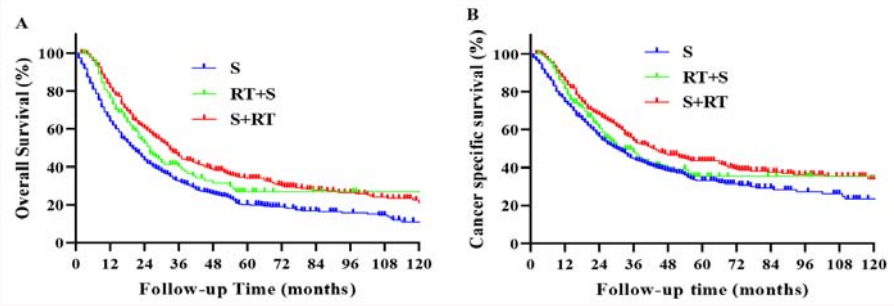

Figure 1: Kaplan-Meier survival curves for overall survival (A) and Cancer Specific Survival (CSS) of the patients with the different treatment types before PSM.

Table 2: Clinicopathological characteristics after covariates were adjusted by PSM.

Characteristics	SA	RT+S	χ^2	P	S	S+RT	χ^2	P	RT+S	S+RT	χ^2	P
	N=138	N=138			N=548	N=548			N=138	N=138		
Race			0.063	0.969			0.068	0.967			0.897	0.837
White	124 (89.9)	125 (90.6)			357 (65.1)	353 (64.4)			108 (78.3)	112 (81.2)		
Black	9 (6.5)	8 (2.9)			77 (14.1)	78 (14.2)			13 (9.4)	10 (7.2)		
Others	5 (3.3)	5 (1.8)			114 (20.8)	117 (21.4)			17 (12.3)	16 (11.6)		
Gender			1.113	0.366			0.092	0.808			0.181	0.777
Male	114 (82.6)	107 (77.5)			298 (54.4)	293 (53.5)			104 (75.4)	107 (77.4)		
Female	24 (17.4)	31 (22.5)			250 (45.6)	255 (46.5)			34 (24.6)	31 (22.5)		
Age (years)			5.331	0.149			7.51	0.057			7.403	0.06
≤ 50	22 (15.9)	23 (16.7)			125 (22.8)	145 (26.5)			38 (27.5)	23 (16.7)		
51~ ≤ 65	54 (39.1)	57 (41.3)			197 (35.9)	220 (40.1)			58 (42)	57 (41.3)		
66~ ≤ 75	40 (29)	48 (34.8)			158 (28.8)	132 (24.1)			31 (22.5)	48 (34.8)		
>75	22 (15.9)	10 (31.3)			68 (12.4)	51 (9.3)			11 (8)	10 (7.2)		
Tumor Site			<0.0001	1			0.257	0.879			9.585	0.137
Cardia/fundus	129 (93.5)	129 (93.5)			127 (23.2)	120 (21.9)			117 (84.8)	120 (86.9)		
body	2 (1.4)	2 (1.4)			99 (18.1)	101 (18.4)			14 (10.1)	11 (8)		
Antrum/pylorus	7 (5.1)	7 (5.1)			322 (58.8)	327 (59.7)			7 (5.1)	7 (5.1)		
Tumor grade			<0.0001	1			0.147	0.849			<0.0001	1
Moderately/highly	4 (2.9)	4 (2.9)			13 (2.4)	15 (2.7)			4 (2.9)	4 (1.4)		
Poorly	134 (97.1)	134 (97.1)			535 (97.6)	533 (97.3)			134 (97.1)	134 (97.1)		
TNM stage			0.132	0.809			0.384	0.577			1.221	0.326
II	63 (45.7)	60 (43.5)			218 (39.8)	208 (38)			51 (37)	60 (43.5)		
III	75 (54.3)	78 (56.5)			330 (60.2)	340 (62)			87 (63)	78 (56.5)		
Depth of infiltration			8.51	0.057			1.341	0.719			0.221	0.86
T1	6 (4.3)	3 (1.1)			16 (2.9)	17 (3.1)			5 (3.6)	3 (2.2)		
T2	57 (41.3)	43 (31.2)			172 (31.4)	189 (34.5)			52 (37.7)	43 (31.2)		
T3	63 (45.7)	86 (62.3)			247 (45.1)	232 (42.3)			60 (43.5)	75 (54.3)		
T4	12 (8.7)	6 (4.3)			113 (20.6)	110 (20.1)			21 (15.2)	17 (12.3)		
Tumor size (mm)			4.74	0.192			0.765	0.858			1.803	0.614
≤ 20	16 (11.6)	20 (14.5)			63 (11.5)	57 (10.4)			14 (10.1)	20 (14.5)		
21~ ≤ 40	41 (29.7)	49 (35.5)			174 (31.8)	172 (31.4)			49 (35.5)	49 (35.5)		
41~ ≤ 60	46 (33.3)	30 (21.7)			136 (24.8)	147 (26.8)			37 (26.8)	30 (21.7)		
>60	35 (25.4)	39 (28.3)			175 (31.9)	172 (31.4)			38 (27.5)	39 (28.3)		

but showed no significant difference when compared with the RT+S group (35.3%). There was no significant difference in CSS between the RT+S group and the S+RT group (Figure 1B).

Outcomes after PSM

After covariates were adjusted by PSM, 138 pairs were matched in the S and RT+S groups, 548 pairs in the S and S+RT groups and

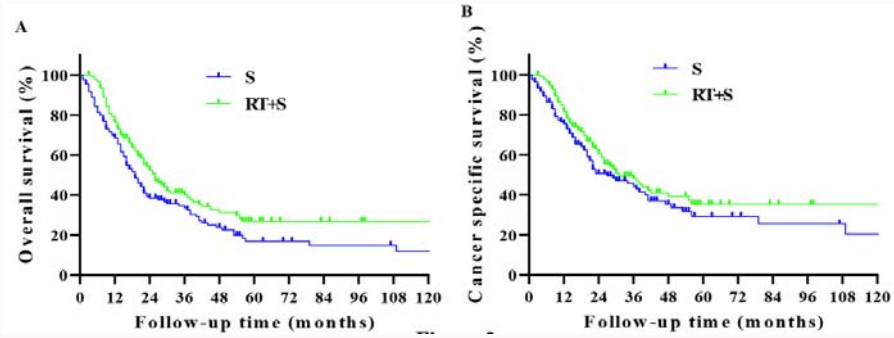

Figure 2: Kaplan-Meier survival curves for overall survival (A) and Cancer Specific Survival (CSS) of the patients with S or RT+S after PSM.

Table 3: Cox regression analysis of overall survival.

Variables	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P	HR (95% CI)	P
Race (Others/Black/White)	0.954 (0.880~1.034)	0.252	-	-
Gender (Female/Male)	0.962 (0.846~1.094)	0.555	-	-
Age (>75/66~ ≤ 75/51~ ≤ 65/≤ 50)	1.312 (1.231~1.398)	<0.0001	1.148 (1.073~1.227)	<0.0001
Tumor Site (Cardiac/Corpus/Antrum)	1.016 (0.945~1.091)	0.671	-	-
Tumor grade (Poorly/Moderately and highly)	1.270 (0.831~1.941)	0.269	-	-
TNM site (III/II)	1.547 (1.354~1.768)	<0.0001	1.452 (1.246~1.691)	<0.0001
Depth of infiltration (T4/T3/T2/T1)	1.261 (1.158~1.374)	<0.0001	1.083 (0.983~1.193)	0.107
Radiotherapy	0.778 (0.727~0.833)	<0.0001	0.799 (0.745~0.857)	<0.0001
(Postoperative/Preoperative /without)				
Tumor size (>60/41~ ≤ 60/21~ ≤ 40/≤ 20)	1.203 (1.128~1.284)	<0.0001	1.148 (1.073~1.227)	<0.0001

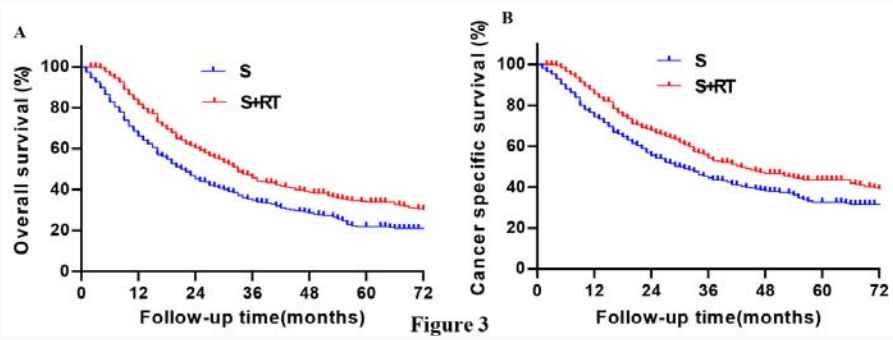

Figure 3

Figure 3: Kaplan-Meier survival curves for overall survival (A) and Cancer Specific Survival (CSS) of the patients with S or S+RT after PSM.

138 pairs in the RT+S and S+RT groups. There were no significant differences in clinicopathological characteristics between the two groups (Table 2). The median survival time in the S and RT+S groups was 19 and 26 months, respectively. The OS rate was 16.5% in the S group, which was significantly lower than that of the RT+S group (26.9%, p=0.012) (Figure 2A). Similar results were obtained for CSS (28.5% *vs.* 35.3%, p=0.085) (Figure 2B). Furthermore, the S+RT group showed a better prognosis than the S group as evidenced by longer OS and CSS (OS, 34.0% *versus* 21.1%, p<0.0001; CSS, 43.6% *vs.* 32.1%, p<0.0001) (Figure 3A, 3B). The prognosis of the RT+S group and S+RT group was not significantly different with the OS being 26.9% and 35.7% respectively (p=0.184) (Figure 4A), and the CSS being 35.3% and 45.8 respectively (p=0.184) (Figure 4B).

Prognostic factors for locally advanced GSRCC

In univariate analysis, age, TNM stage, depth of infiltration, radiotherapy and tumor size were significant prognostic factors for OS and CSS in patients with locally advanced GSRCC. Multivariate analysis identified age, TNM stage, and radiotherapy and tumor size as independent prognostic factors for survival (Table 3, 4).

Discussion

Based on research conclusions from previous studies, the prognosis of GSRCC remains controversial [8-10]. In early GC, the prognosis of GSRCC is better than that of non-GSRCC; however, in advanced stages, the prognosis of GSRCC is worse than that of non-GSRCC. Several reports have shown that a high risk of lymph node metastasis and early peritoneal dissemination could be associated with a worse prognosis [9,11], due to CDH1-gene mutations and E-cadherin deficiency [12]. Some studies suggest that GSRCC is insensitive to chemotherapy, neither postoperative nor preoperative chemotherapy improves prognosis [2,9,11,13,14]. Several trials such

Table 4: Cox regression analysis of cancer specific survival.

Variables	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P	HR (95% CI)	P
Race (Others/Black/White)	0.979 (0.892~1.076)	0.664	-	-
Gender (Female/Male)	0.925 (0.796~1.075)	0.311	-	-
Age (>75/66~ ≤ 75/51~ ≤ 65/≤ 50	1.131 (0.049~1.219)	0.001	1.095 (1.016~1.181)	0.018
Tumor Site (Cardiac/Corpus/Antrum)	0.988 (0.908~1.074)	0.774	-	-
Tumor grade (Poorly/Moderately and highly)	1.698 (0.958~3.011)	0.07	-	-
TNM site (III/II)	1.908 (1.623~2.245)	<0.0001	1.710 (1.424~2.054)	<0.0001
Depth of tumor invasion (T4/T3/T2/T1)	1.330 (1.203~1.471)	<0.0001	1.091 (0.974~1.223)	0.133
Radiotherapy (Postoperative/Preoperative /without)	0.826 (0.762~0.894)	<0.0001	0.817 (0.753~0.887)	<0.0001
Tumor size (>60/41~ ≤ 60/21~ ≤ 40/≤ 20)	1.292 (1.196~1.396)	<0.0001	1.216 (1.123~1.317)	<0.0001

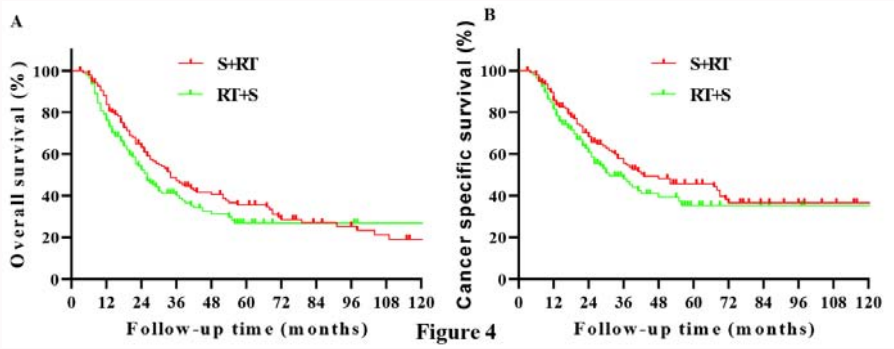

Figure 4: Kaplan-Meier survival curves for overall survival (A) and Cancer Specific Survival (CSS) of the patients with RT+S or S+RT after PSM.

as ARTIST [15] and INT0116 [16] have proven that radiotherapy can improve the prognosis of gastric adenocarcinoma.

However, trials targeting the efficacy of radiotherapy in GSRCC patients are scanty and the specific regimens for GSRCC remain uncertain. A previous study using the same database to extract eligible patients but only compare those with and without preoperative radiotherapy has shown that preoperative radiotherapy is associated with significant survival benefits for the patients with advanced GSRCC [17]. In the present study, we divided the study population and the outcomes into three different groups (surgery alone, surgery + pre-operative radiotherapy and surgery + post-operative radiotherapy) thus giving a broader look on the topic. We found that compared with surgery alone, postoperative radiotherapy may improve the prognosis of GSRCC patients, which is consistent with another previous study based on the SEER database [11]. However, these conclusions remain disputed. Zhu et al. [18] reported that adjuvant chemoradiotherapy was associated with poor survival compared with adjuvant chemotherapy in GSRCC patients with D2 gastrectomy, with a median follow-up of 80.5 months and the 3-year OS rate was significantly higher in the chemotherapy group (70.5% *vs.* 58.6, HR=0.633, p=0.017). Hence, further research should be undertaken to clarify this discrepancy.

Contrary to expectations, we found that preoperative radiotherapy did not improve the CSS compared to surgery alone and that postoperative radiotherapy showed a slightly better prognosis than preoperative radiotherapy. This could be owing to the fact that adjacent organs such as the liver and duodenum can reduce the dosage of radiation on lymph node drainage regions. Another possible explanation is that there is still no comprehensive understanding of lymph node drainage region in GSRCC and target regions of GSRCC have not achieved consensus, which may lead to the inaccuracy of radiotherapy. Currently, most studies do not offer compelling evidence on this issue; therefore, more randomized controlled trials are required in further studies.

Furthermore, using univariate and multivariate analyses, we found that the TNM stage was an independent prognostic factor and depth of infiltration was excluded by multivariate analysis. This result suggested that compared with the T stage, lymph node metastasis was considered to be a significant prognostic factor, which was consistent with conclusions from previous related researches [19,20]. Besides, tumor size is another important factor affecting prognosis and lymph node metastasis. Jun et al. [21] suggested that tumor size over 3.5 cm was an independent risk factor for GC patients. An et al. [22] observed 1043 cases of submucosa infiltration in early GC and found that a tumor diameter over 2 cm was an independent risk factor for lymph node metastasis. Consistent with these researches, we found that tumor size was also an important prognostic factor in patients with GSRCC.

In conclusion, compared with surgery alone, surgery combined with preoperative or postoperative radiotherapy is beneficial to the long-term survival of patients with locally advanced GSRCC. Further exploration is warranted to optimize the application of radiotherapy in GSRCC.

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