

## Research Article

# Radiotherapy Improves the Prognosis in Signet Ring Cell Carcinoma and Non-Signet Ring Cell Gastric Adenocarcinoma Patients: A SEER Database Analysis

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## Abstract

**Objective:** To investigate the effect of radiotherapy on prognosis in gastric signet ring cell carcinoma (SRCC) and gastric non-signet ring cell adenocarcinoma (NSRCC) patients.

**Methods:** A total of 23,971 patients diagnosed with gastric cancer were collected from 2004 to 2013 by SEER database, including 17,679 NSRCC patients and 6,292 SRCC patients. Patients were divided to two groups and compared according to whether radical gastrectomy was performed on them. After clinic pathological characteristics of the two groups were balanced by the propensity score matching (PSM) method, survival rates of the two groups were then compared.

**Results:** The Over Survival (OS) and Cancer-Specific Survival (CSS) time of SRCC and NSRCC patients in the radiotherapy group were significantly better than those in the non-radiotherapy group. But the clinical and pathological characteristics (gender, age, pathological differentiation degree, T stage, N stage, and metastasis) of the two groups were significantly unbalanced ( $p < 0.001$ ). After 1:1 PSM matching, it was found that radiotherapy had no significant effect on OS and CSS time of NSRCC patients, but radiotherapy could significantly improve OS and CSS time of SRCC patients.

**Conclusion:** SRCC patients are more sensitive to radiotherapy than NSRCC patients. Although the prognosis of SRCC is far less than that of NSRCC patients, the treatment strategy of surgical resection of primary lesions combined with radiotherapy should be recommend for SRCC patients, and whether radiotherapy benefits NSRCC patients still needs to be further studied.

**Keywords:** Over Survival; NSRCC; Cancer-Specific Survival; gastric cancer; SEER; Radiotherapy

## Abbreviations

SRCC: Signet Ring Cell Carcinoma; NSRCC: Non-Signet Ring Cell Adenocarcinoma; PSM: Propensity Score Matching; OS: Over Survival; CSS: Cancer-Specific Survival Time

## Introduction

Gastric Cancer (GC) is the fourth - common malignant tumor in the world and is the third leading cause of cancer-related death [1]. Gastric carcinoma has many histological types and classifications, such as Lauren [2], Japanese [3] and Ming classifications [4]. Among of all these classifications, each histological type has its own characteristics. Therefore, different histological types of gastric cancer might determine they have different treatment strategies. Adenocarcinoma is the most common pathological type of gastric cancer and it includes a special type named as Signet Ring Cell Carcinoma gastric carcinoma (SRCC), which accounts for 15.1-28.2 % of gastric cancer [5]. SRCC was once thought to be a histological type characterized with poor prognosis and high possibility of infiltrating the stomach [6]. Therefore, SRCC has been widely reported as an independent predictor of poor prognosis especially in Western countries. The

majority of these tumors are diagnosed at an advanced stage, with higher lymph node metastasis rates, higher incidence of peritoneal cancer and lower chemotherapy sensitivity [7]. SRCC is considered a unique pathological entity in the pathological types of gastric cancer. Some studies have shown that SRCC is always associated with the rejuvenation, higher stage of differentiation and lower survival rate compared to gastric adenocarcinoma [8].

In recent years, treatment levels in gastric cancer patients have been rapidly improved especially for local advanced gastric cancers. The United States NCCN Guide or the European ESMO Guidelines recommended perioperative radiotherapy and chemotherapy treatment model, so the therapeutic effect of local advanced gastric cancer has been improved obviously. With the development and widespread popularization of D2 surgery, the indications of radiotherapy and the scope of radiotherapy have become the scholars' focus [9]. Radiotherapy can be used for early shrinkage of tumors before surgery and can help improve the likelihood of therapeutic resection [10]. In gastric cancer patients with distant metastasis, it is recommended that some treatment methods such as irradiating the primary focus or metastatic cooker to reduce the obstruction,

compression, bleeding or pain should be carried out in order to improve the life quality of patients. A large amount of samples data show that adjuvant radiotherapy can effectively improve the survival and prognosis of gastric adenocarcinoma patients [11]. In clinical practices, it could be found that the effects of radiotherapy in Non-Signet Rings Cell Gastric Adenocarcinoma (NSRCC) and SRCC patients are different. A retrospective study on two large samples found that in phase II and III, rectal ring cell carcinoma patients undergoing radiotherapy had a statistically worse CSS time than rectal non-ring cell carcinoma patients [12], indicating that in SRCC and NSRCC patients there might also be differences in the sensitivity to radiotherapy. In order to explore the effect of radiotherapy on gastric SRCC and NSRCC patients, we selected and studied the patients with gastric cancer through SEER database and divided them into SRCC and NSRCC patients according to the pathological types of gastric cancer. By comparing the effect of radiotherapy on the survival and prognosis of SRCC and NSRCC patients, we can provide a basis for clinical rational application of radiotherapy.

## Materials and Methods

### Patient samples collection

In this study, we investigated the clinical value of radiotherapy for SRCC and NSRCC patients using SEER database (<http://seer.cancer.gov/about/overview.html>), which is maintained by the National Cancer Institute and includes 18 population-based cancer registries with information of cancer morbidity and mortality in the United States [13]. This version of the SEER database we used was released in April 2014 (submitted in November 2013). All TNM classifications are defined according to the criteria described in the Cancer staging manual of the United States Joint Commission on Cancer (AJCC) (6th edition 2004, Paras. I, II, III and IV). Histological classifications were divided into well differentiation (G1), moderately differentiation (G2), poor differentiation (G3) and un-differentiation (G4) groups. CSS time was calculated from the diagnosis beginning date to the specific death date of tumor patients or the end date of follow-up. SEER database includes the diagnostic information such as age, sex, race, years of diagnosis, numbers of tumors, tumors size, TNM staging, histological type, histological classification, surgical and radiotherapy status for each patient. Tumors are classified according to the International Classification of Tumor Diseases (ICD-O). We obtained 150,265 patients who were encoded as the primary site of "stomach", excluding patients without pathological diagnosis (n=7432), patients without pathological staging (n=40193), patients with pathology as simple parasites (n=167), patients with pathological diagnosis of cancer only (n=2656), patients with pathological diagnosis of neuroendocrine tumor (n=1604), patients lack of TMN staging (n=74242). Finally, 23,971 patients was included in our study. Of these, there are 17,679 NSRCC patients and 6,292 SRCC patients. The group comparison was carried out according to whether radical resection was performed on these patients.

### Ethics Statement

This study is conducted based on data from the public SEER database, which does not contain any identifiers. Due to the retrospective nature of the study, the patient's informed consent is not required. The analysis does not involve interactions with human subjects or use their personally identifiable information. Prior to

the analysis, patient records/information are anonymous and de-identified, and these methods are in accordance with the guidelines of the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region. This study protocol was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region.

### Statistical analysis

Compare classification variables between two treatment groups using Pearson's  $\chi^2$  for statistical analysis, while discontinuous variables use ANOVA. The survival curve is calculated by Kaplan-Meier method and the Log-rank test is compared. When the survival curve is intersected and  $p < 0.05$ , the intersection is obtained by landmark. Discovery and the segmented statistical analysis is carried out according to the pvalue of each segment [14]. Cox proportional risk regression model is used to identify the risk factors that affects CSS and OS time independently in gastric SRCC and NSRCC patients. The effect of radiotherapy on the survival prognosis of SRCC and NSRCC is compared by tendency score matching analysis (propensity score-matched analyses, PSM). The nearest neighbor matching method is used to complete the one-to-one match (age, sex, race, years of diagnosis, numbers of tumors, tumors size, TNM staging, histological type, histological classification and other variables) without replacement. Caliper width is 0.05 times the standard deviation of the tendentious score logit, and it is estimated that the co-construction variable deviation of  $>99\%$  can be eliminated [15].

## Results

### Patient characteristics

A total of 23971 GC patients were included in this study, most of them were diagnosed with NSRCC (n=17679, 73.75%). There are more people diagnosed at age  $< 65$  years in the SRCC group than in the NSRCC group (54.52% vs. 37.89%,  $p < 0.001$ ). The occurrence frequency of low differentiation tumors in SRCC patients was also higher than that in NSRCC patients (97.35% vs. 59.66%,  $p < 0.001$ ). And the frequency of lymph node metastasis in SRCC patients was higher than that in NSRCC patients (57.54% vs. 52.39%,  $p < 0.001$ ). Moreover, the frequency of distant metastasis in SRCC patients was higher than that in NSRCC patients (45.01% vs. 26.39%,  $p < 0.001$ ). In addition, the SRCC group contained more female patients (48.90% vs. 31.01%,  $p < 0.001$ ) (Table 1-4).

### Prognostic factors in SRCC and NSRCC patients

The multivariate analysis results of all SRCC and NSRCC patients using Cox model are shown in Table 5 and 6. From the data, we can see that older ( $> 65$  years old), larger the tumor size ( $> 1$ cm) and lower the degree of tumor differentiation lead to shorter survival time of SRCC and NSRCC patients ( $p < 0.001$ ). Besides, whether to carry out gastrectomy or radiotherapy and distant metastasis degree are also important factors affecting the survival time in SRCC and NSRCC patients. However, each factor has some different effects on SRCC and NSRCC patients. For example, the degree of tumor differentiation is not an independent risk factor affecting the prognosis of SRCC patients, but it is an independent risk factor for NSRCC patients. For both SRCC and NSRCC patients, radiotherapy has prolonged their survival time obviously, but there are still some differences between them. The univariate analysis of OS time show that radiotherapy for

**Table 1:** Demographics according to radiotherapy vs. non-radiotherapy for NSRCC patients without gastrectomy.

	Unadjusted					Adjusted				
	Non-rad	SD/%	Rad	SD/%	p	Non-rad	SD/%	Rad	SD/%	p
No.	5157	68.82%	2336	31.18%	-	709	50%	709	50%	-
<b>Gender</b>										
Male	3397	65.87%	1811	77.53%	<0.001	598	84.34%	598	84.34%	0.990
Female	1760	34.13%	525	22.47%		111	15.66%	111	15.66%	
<b>Age (yrs)</b>										
≥65	1828	35.45%	823	35.23%	0.856	217	30.61%	217	30.61%	0.984
<65	3329	64.55%	1513	64.77%		492	69.39%	492	69.39%	
<b>Insurance</b>										
Uninsured	608	11.79%	207	8.86%	<0.001	16	2.26%	16	2.26%	1.000
Insured	2980	57.79%	1489	63.74%		532	75.04%	532	75.04%	
Unknown	1569	30.42%	640	27.40%		161	22.71%	161	22.71%	
<b>Tumor Grade</b>										
1	265	5.14%	117	5.01%	<0.001	23	3.24%	23	3.24%	1.000
2	1744	33.82%	886	37.93%		247	34.84%	247	34.84%	
3	3090	59.92%	1300	55.65%		436	61.50%	436	61.50%	
4	58	1.12%	33	1.41%		3	0.42%	3	0.42%	
<b>Race</b>										
Black	801	15.53%	201	8.60%	<0.001	11	1.55%	11	1.55%	1.000
other	597	11.58%	174	7.45%		14	1.97%	14	1.97%	
White	3743	72.58%	1957	83.78%		684	96.47%	684	96.47%	
unknown	16	0.31%	4	0.17%		0	0.00%	0	0.00%	
<b>Marital Status</b>										
Divorced	429	8.32%	206	8.82%	<0.001	29	4.09%	29	4.09%	1.000
Married	2657	51.52%	1447	61.94%		537	75.74%	537	75.74%	
Separated	57	1.11%	21	0.90%		0	0.00%	0	0.00%	
Single	739	14.33%	252	10.79%		47	6.63%	47	6.63%	
Widowed	259	5.02%	75	3.21%		10	1.41%	10	1.41%	
unknown	1016	19.70%	335	14.34%		86	12.13%	86	12.13%	
<b>Primary Site</b>										
Cardia	1909	37.02%	1785	76.41%	<0.001	611	86.18%	611	86.18%	1.000
Fundus of Stomach	246	4.77%	56	2.40%		5	0.71%	5	0.71%	
Body of Stomach	459	8.90%	72	3.08%		16	2.26%	16	2.26%	
Gastric Antrum	836	16.21%	125	5.35%		34	4.80%	34	4.80%	
Pylorus	109	2.11%	14	0.60%		0	0.00%	0	0.00%	
Lesser Curvature of Stomach	344	6.67%	61	2.61%		4	0.56%	4	0.56%	
Greater Curvature of Stomach	153	2.97%	26	1.11%		2	0.28%	2	0.28%	
Overlapping Lesion of Stomach	387	7.50%	86	3.68%		8	1.13%	8	1.13%	
Stomach	714	13.85%	111	4.75%		29	4.09%	29	4.09%	
<b>T Stage (AJCC, 2004)</b>										
T0	6	0.12%	1	0.04%	<0.001	0	0.00%	0	0.00%	1.000
T1	2633	51.06%	774	33.13%		379	53.46%	379	53.46%	
T2a	318	6.17%	264	11.30%		45	6.35%	45	6.35%	
T2b	667	12.93%	581	24.87%		123	17.35%	123	17.35%	
T3	320	6.21%	350	14.98%		69	9.73%	69	9.73%	
T4	1213	23.52%	366	15.67%		93	13.12%	93	13.12%	

<b>N Stage (AJCC, 2004)</b>										
N0	3168	61.43%	1093	46.79%	<0.001	389	54.87%	389	54.87%	0.998
N1	1788	34.67%	1085	46.45%		306	43.16%	306	43.16%	
N2	146	2.83%	128	5.48%		13	1.83%	13	1.83%	
N3	55	1.07%	30	1.28%		1	0.14%	1	0.14%	
<b>M Stage (AJCC, 2004)</b>										
M0	2445	47.41%	1528	65.41%	<0.001	411	57.97%	411	57.97%	1.000
M1	2715	52.65%	808	34.59%		298	42.03%	298	42.03%	
<b>Tumor Size</b>										
≤1cm	2002	38.82%	1238	53.00%	<0.001	352	49.65%	352	49.65%	1.000
>1cm	3155	61.18%	1098	47.00%		357	50.35%	357	50.35%	

**Table 2:** Demographics according to radiotherapy vs. non-radiotherapy for SRCC patients without gastrectomy.

	<b>Unadjusted</b>					<b>Adjusted</b>				
	<b>Non-rad</b>	<b>SD/%</b>	<b>Rad</b>	<b>SD/%</b>	<b>p</b>	<b>Non-rad</b>	<b>SD/%</b>	<b>Rad</b>	<b>SD/%</b>	<b>p</b>
No.	1705	79.23%	447	20.77%	-	81	50%	81	50%	-
<b>Gender</b>										
Male	864	50.67%	1784	50.40%	<0.001	60	74.07%	60	74.07%	1.000
Female	841	49.33%	1756	49.60%		21	25.93%	21	25.93%	
<b>Age (yrs)</b>										
≥65	918	53.84%	1858	52.49%	<0.001	32	39.51%	32	39.51%	0.980
<65	787	46.16%	1682	47.51%		49	60.49%	49	60.49%	
<b>Insurance</b>										
Uninsured	242	14.19%	523	14.77%	<0.001	2	2.47%	2	2.47%	1.000
Insured	947	55.54%	1785	50.42%		64	79.01%	64	79.01%	
Unknown	516	30.26%	1232	34.80%		15	18.52%	15	18.52%	
<b>Tumor Grade</b>										
1	3	0.18%	6	0.17%	<0.001	0	0.00%	0	0.00%	1.000
2	39	2.29%	72	2.03%		0	0.00%	0	0.00%	
3	1617	94.84%	3378	95.42%		81	100%	81	100%	
4	46	2.70%	84	2.37%		0	0.00%	0	0.00%	
<b>Race</b>										
Black	254	14.90%	443	12.51%	<0.001	2	2.47%	2	2.47%	1.000
Other	232	13.61%	509	14.38%		5	6.17%	5	6.17%	
White	1211	71.03%	2564	72.43%		74	91.36%	74	91.36%	
Unknown	8	0.47%	24	0.68%		0	0.00%	0	0.00%	
<b>Marital Status</b>										
Divorced	156	9.15%	289	8.16%	<0.001	0	0.00%	0	0.00%	1.000
Married	899	52.73%	1816	51.30%		62	76.54%	62	76.54%	
Separated	17	1.00%	39	1.10%		0	0.00%	0	0.00%	
Single	297	17.42%	624	17.63%		6	7.41%	6	7.41%	
Widowed	72	4.22%	571	16.13%		1	1.23%	1	1.23%	
Unknown	264	15.48%	201	5.68%		12	14.81%	12	14.81%	
<b>Primary Site</b>										

Cardia	296	17.36%	576	16.27%	<0.001	47	50.72%	47	50.72%	1.000
Fundus of Stomach	73	4.28%	144	4.07%		2	1.45%	2	1.45%	
Body of Stomach	229	13.43%	505	14.27%		5	5.80%	5	5.80%	
Gastric Antrum	341	20.00%	655	18.50%		7	10.87%	7	10.87%	
Pylorus	33	1.94%	71	2.01%		1	0.72%	1	0.72%	
Lesser Curvature of Stomach	98	5.75%	199	5.62%		2	2.90%	2	2.90%	
Greater Curvature of Stomach	69	4.05%	127	3.59%		2	1.45%	2	1.45%	
Overlapping Lesion of Stomach	238	13.96%	424	11.98%		5	5.07%	5	5.07%	
Stomach	328	19.24%	839	23.70%		10	21.01%	10	21.01%	
<b>T Stage (AJCC, 2004)</b>										
T0	5	0.29%	6	0.17%	<0.001	0	0.00%	0	0.00%	1.000
T1	622	36.48%	725	20.48%		40	49.38%	40	49.38%	
T2a	183	10.73%	235	6.64%		2	2.47%	2	2.47%	
T2b	245	14.37%	288	8.14%		14	17.28%	14	17.28%	
T3	159	9.33%	195	5.51%		5	6.17%	5	6.17%	
T4	491	28.80%	650	18.36%		20	24.69%	20	24.69%	
<b>N Stage (AJCC, 2004)</b>										
N0	1089	63.87%	1562	44.12%	<0.001	49	60.49%	49	60.49%	1.000
N1	553	32.43%	784	22.15%		32	39.51%	32	39.51%	
N2	33	1.94%	41	1.16%		0	0.00%	0	0.00%	
N3	30	1.76%	34	0.96%		0	0.00%	0	0.00%	
<b>M Stage (AJCC, 2004)</b>										
M0	693	40.65%	986	27.85%	<0.001	42	51.85%	42	51.85%	1.000
M1	2101	59.35%	2139	60.42%		39	48.15%	39	48.15%	
<b>Tumor Size</b>										
≤1cm	437	25.63%	729	20.59%	<0.001	24	29.63%	24	29.63%	1.000
>1cm	1268	74.37%	2811	79.41%		57	70.37%	57	70.37%	

**Table 3:** Demographics according to radiotherapy vs. non-radiotherapy for NSRCC patients with gastrectomy.

	Unadjusted					Adjusted				
	Non-rad	SD/%	Rad	SD/%	p	Non-rad	SD/%	Rad	SD/%	p
No.	6804	66.79%	3382	33.21%	-	132	50%	132	50%	-
<b>Gender</b>										
Male	4447	65.36%	2541	75.13%	<0.001	124	93.94%	124	93.94%	0.990
Female	2357	34.64%	841	24.87%		8	6.06%	8	6.06%	
<b>Age (yrs)</b>										
≥65	2160	31.75%	1888	55.82%	<0.001		31.06%	41	31.06%	0.984
<65	4644	68.25%	1494	44.18%		91	68.94%	91	68.94%	
<b>Insurance</b>										
Uninsured	694	10.20%	278	8.22%	<0.001	0	0.00%	0	0.00%	1.000
Insured	3563	52.37%	1937	57.27%		112	84.85%	112	84.85%	
Unknown	2547	37.43%	1167	34.51%		20	15.15%	20	15.15%	
<b>Tumor Grade</b>										
1	509	7.48%	123	3.64%	<0.001	4	3.03%	4	3.03%	1.000
2	2378	34.95%	1109	32.79%		54	40.91%	54	40.91%	
3	3789	55.69%	2073	61.30%		74	56.06%	74	56.06%	
4	128	1.88%	77	2.28%		0	0.00%	0	0.00%	

Race										
Black	909	13.36%	369	10.91%	<0.001	0	0.00%	0	0.00%	1.000
other	1202	17.67%	500	14.78%		0	0.00%	0	0.00%	
White	4671	68.65%	2508	74.16%		0	0.00%	0	0.00%	
unknown	22	0.32%	5	0.15%		132	100.00%	132	100.00%	
<b>Marital Status</b>										
Divorced	45	0.66%	277	8.19%	<0.001	1	0.76%	1	0.76%	1.000
Married	4068	59.79%	2334	69.01%		121	91.67%	121	91.67%	
Separated	73	1.07%	34	1.01%		0	0.00%	0	0.00%	
Single	785	11.54%	369	10.91%		3	2.27%	3	2.27%	
Widowed	228	3.35%	89	2.63%		0	0.00%	0	0.00%	
Unknown	1175	17.27%	279	8.25%		7	5.30%	7	5.30%	
<b>Primary Site</b>										
Cardia	1951	28.67%	1762	52.10%	<0.001	131	99.24%	131	99.24%	1.000
Fundus of Stomach	191	2.81%	81	2.40%		0	0.00%	0	0.00%	
Body of Stomach	541	7.95%	176	5.20%		0	0.00%	0	0.00%	
Gastric Antrum	1734	25.49%	531	15.70%		0	0.00%	0	0.00%	
Pylorus	308	4.53%	117	3.46%		0	0.00%	0	0.00%	
Lesser Curvature of Stomach	741	10.89%	271	8.01%		0	0.00%	0	0.00%	
Greater Curvature of Stomach	326	4.79%	125	3.70%		0	0.00%	0	0.00%	
Overlapping Lesion of Stomach	368	5.41%	140	4.14%		0	0.00%	0	0.00%	
Stomach	644	9.47%	179	5.29%		1	0.76%	1	0.76%	
<b>T Stage (AJCC, 2004)</b>										
T0	0	0.00%	0	0.00%	<0.001	0	0.00%	0	0.00%	1.000
T1	1981	29.12%	287	8.49%		46	34.85%	46	34.85%	
T2a	911	13.39%	442	13.07%		16	12.12%	16	12.12%	
T2b	2083	30.61%	1429	42.25%		40	30.30%	40	30.30%	
T3	1194	17.55%	956	28.27%		26	19.70%	26	19.70%	
T4	635	9.33%	268	7.92%		4	3.03%	4	3.03%	
<b>N Stage (AJCC, 2004)</b>										
N0	3337	49.04%	818	24.19%	<0.001	61	46.21%	61	46.21%	0.998
N1	2223	32.67%	1833	54.20%		67	50.76%	67	50.76%	
N2	849	12.48%	562	16.62%		4	3.03%	4	3.03%	
N3	395	5.81%	169	5.00%		0	0.00%	0	0.00%	
<b>M Stage (AJCC, 2004)</b>										
M0	5873	86.32%	3168	93.67%	<0.001	119	90.15%	119	90.15%	1.000
M1	931	13.68%	214	6.33%		13	9.85%	13	9.85%	
<b>Tumor Size</b>										
≤1cm	6035	88.70%	2895	85.60%	<0.001	99	75.00%	99	75.00%	1.000
>1cm	769	11.30%	487	14.40%		33	25.00%	33	25.00%	

SRCC patients (HR, 1.501; 95% CI, 1.405-1.602; p<0.001) is better than that for NSRCC patients (HR, 1.356; 95% CI, 1.304-1.410; p<0.001). But from the multivariate analysis data, we can know that radiotherapy for SRCC (HR, 1.352; 95% CI, 1.258-1.453; p<0.001) and NSRCC (HR, 1.405; 95% CI, 1.347-1.466; p<0.001) is not far apart.

The univariate analysis of CSS time show that radiotherapy

has also better effects on SRCC patients (HR, 1.413; 95% CI, 1.311-1.523; p<0.001) than NSRCC patients (HR, 1.250; 95% CI, 1.193-1.309; p<0.001). From the multivariate analysis, we can also know radiotherapy for SRCC (HR, 1.254; 95% CI, 1.155-1.361; p<0.001) and NSRCC (HR, 1.326; 95% CI, 1.260-1.395; p<0.001) is also not far apart.

**Table 4:** Demographics according to radiotherapy vs. non-radiotherapy for SRCC patients with gastrectomy.

	Unadjusted					Adjusted				
	Non-rad	SD/%	Rad	SD/%	p	Non-rad	SD/%	Rad	SD/%	p
No.	2720	0.657	1420	0.343	-	291	0.5	291	0.5	-
<b>Gender</b>										
Male	1377	0.5063	773	0.5425	<0.001	186	0.6392	186	0.6392	1.000
Female	1343	0.4938	652	0.4575		105	0.3608	105	0.3608	
<b>Age (yrs)</b>										
≥65	1400	0.5147	944	0.6625	<0.001	182	0.6254	182	0.6254	0.984
<65	1320	0.4853	481	0.3375		109	0.3746	109	0.3746	
<b>Insurance</b>										
Uninsured	293	0.1077	146	0.1025	<0.001	11	0.0378	11	0.0378	1.000
Insured	1431	0.5261	742	0.5207		193	0.6632	193	0.6632	
Unknown	996	0.3662	537	0.3768		87	0.299	87	0.299	
<b>Tumor Grade</b>										
1	7	0.0026	6	0.0042	<0.001	0	0	0	0	1.000
2	78	0.0287	38	0.0267		2	0.0069	2	0.0069	
3	2532	0.9309	1324	0.9291		287	0.9863	287	0.9863	
4	103	0.0379	57	0.04		2	0.0069	2	0.0069	
<b>Race</b>										
Black	307	0.1129	177	0.1242	<0.001	9	0.0309	9	0.0309	1.000
other	526	0.1934	281	0.1972		39	0.134	39	0.134	
White	1877	0.6901	961	0.6744		243	0.8351	243	0.8351	
unknown	10	0.0037	6	0.0042		0	0	0	0	
<b>Marital Status</b>										
Divorced	213	0.0783	117	0.0821	<0.001	7	0.0241	7	0.0241	1.000
Married	1639	0.6026	938	0.6582		247	0.8488	247	0.8488	
Separated	30	0.011	17	0.0119		0	0	0	0	
Single	383	0.1408	195	0.1368		18	0.0619	18	0.0619	
Widowed	101	0.0371	45	0.0316		3	0.0103	3	0.0103	
unknown	354	0.1301	113	0.0793		16	0.055	16	0.055	
<b>Primary Site</b>										
Cardia	298	0.1096	295	0.207	<0.001	72	0.2474	72	0.2474	1.000
Fundus of stomach	69	0.0254	40	0.0281		3	0.0103	3	0.0103	
Body of stomach	312	0.1147	132	0.0926		30	0.1031	30	0.1031	
Gastric antrum	784	0.2882	386	0.2709		105	0.3608	105	0.3608	
Pylorus	110	0.0404	66	0.0463		1	0.0034	1	0.0034	
Lesser curvature of stomach	350	0.1287	180	0.1263		34	0.1168	34	0.1168	
Greater curvature of stomach	172	0.0632	69	0.0484		6	0.0206	6	0.0206	
Overlapping lesion of stomach	315	0.1158	131	0.0919		28	0.0962	28	0.0962	
stomach	310	0.114	126	0.0884		12	0.0412	12	0.0412	
<b>T Stage (AJCC, 2004)</b>										
T0	662	0.2434	0	0	<0.001	0	0	0	0	1.000
T1	217	0.0798	97	0.0681		25	0.0859	25	0.0859	
T2a	731	0.2688	150	0.1053		22	0.0756	22	0.0756	
T2b	747	0.2746	558	0.3916		127	0.4364	127	0.4364	
T3	338	0.1243	477	0.3347		104	0.3574	104	0.3574	
T4	25	0.0092	143	0.1004		13	0.0447	13	0.0447	

N Stage (AJCC, 2004)										
N0	1065	0.3915	271	0.1902	<0.001	59	0.2027	59	0.2027	1.000
N1	777	0.2857	647	0.454		137	0.4708	137	0.4708	
N2	537	0.1974	362	0.254		71	0.244	71	0.244	
N3	341	0.1254	145	0.1018		24	0.0825	24	0.0825	
M Stage (AJCC, 2004)										
M0	2145	0.7886	1340	0.9404	<0.001	283	0.9725	283	0.9725	1.000
M1	565	0.2077	85	0.0596		8	0.0275	8	0.0275	
Tumor Size										
≤1cm	2215	0.8143	1187	0.833	<0.001	272	0.9347	272	0.9347	1.000
>1cm	505	0.1857	238	0.167		19	0.0653	19	0.0653	

**Table 5:** Univariate and Multivariate Cox Analyses of SRCC Patients According to Various Clinic pathological Variables.

Variable	Overall Survival				Cancer-Specific Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
<b>Gender</b>		0.251				0.94		
Male	Reference		-		Reference		-	
Female	1.023(0.984-1.063)	0.294	-	-	0.997(0.931-1.068)	0.94	-	-
<b>Age</b>		<0.001				0.201		
<65	Reference		Reference		Reference		-	
≥65	1.358(1.280-1.441)	<0.001	1.515(1.454-1.578)	<0.001	1.046(0.976-1.121)	0.201	-	-
<b>Insurance</b>		0.055				0.054		
Uninsured	Reference		Reference	-	-		-	
Insured	0.991(0.842-1.167)	0.915	0.934(0.777-1.122)	-	-	0.463	-	-
Unknown	1.071(0.906-1.265)	0.421	1.020(0.846-1.231)	-	-	0.834	-	-
<b>Tumor Grade</b>		0.131				0.071		
1	Reference		Reference	-	-		-	
2	2.136(1.044-4.369)	0.038	1.854(0.808-4.251)	-	-	0.145	-	-
3	2.255(1.127-4.513)	0.022	2.248(1.009-5.008)	-	-	0.047	-	-
4	2.278(1.120-4.635)	0.023	2.343(1.032-5.316)	-	-	0.042	-	-
<b>Race</b>		<0.001				<0.001		
Black	Reference		Reference				Reference	
Other	0.725(0.648-0.811)	<0.001	0.807(0.719-0.906)	<0.001	0.750(0.659-0.855)	<0.001	0.876(0.767-1.001)	0.051
Unknown	1.027(0.939-1.124)	0.555	0.955(0.870-1.048)	0.327	1.040(0.936-1.154)	0.467	1.013(0.910-1.128)	0.815
White	0.397(0.188-0.836)	0.015	0.428(0.203-0.904)	0.026	0.457(0.204-1.023)	0.057	0.524(0.234-1.176)	0.117
<b>Marital Status</b>		<0.001				<0.001		
Divorced	Reference		Reference		Reference		Reference	
Married	0.926(0.830-1.034)	0.174	0.917(0.820-1.025)	0.126	0.965(0.849-1.098)	0.59	0.976(0.858-1.111)	0.714
Separated	0.812(0.585-1.125)	0.21	0.917(0.661-1.272)	0.604	0.912(0.635-1.310)	0.619	1.052(0.732-1.512)	0.786
Single	1.061(0.933-1.207)	0.368	1.003(0.881-1.142)	0.967	1.157(0.998-1.342)	0.054	1.062(0.914-1.232)	0.433
Widowed	1.368(1.202-1.556)	<0.001	1.209(1.058-1.382)	0.005	1.220(1.046-1.423)	0.012	1.319(1.129-1.541)	<0.001
Other	1.005(0.831-1.216)	0.958	0.955(0.788-1.157)	0.64	0.993(0.795-1.242)	0.954	1.008(0.806-1.262)	0.942
<b>T Stage (AJCC, 2004)</b>		<0.001				<0.001		
T0	Reference		Reference		Reference		Reference	
T1	0.260(0.117-0.581)	0.001	0.665(0.295-1.495)	0.323	0.267(0.100-0.715)	0.009	0.725(0.269-1.954)	0.525
T2a	0.244(0.109-0.546)	0.001	0.661(0.292-1.494)	0.319	0.235(0.087-0.633)	0.004	0.657(0.242-1.783)	0.409

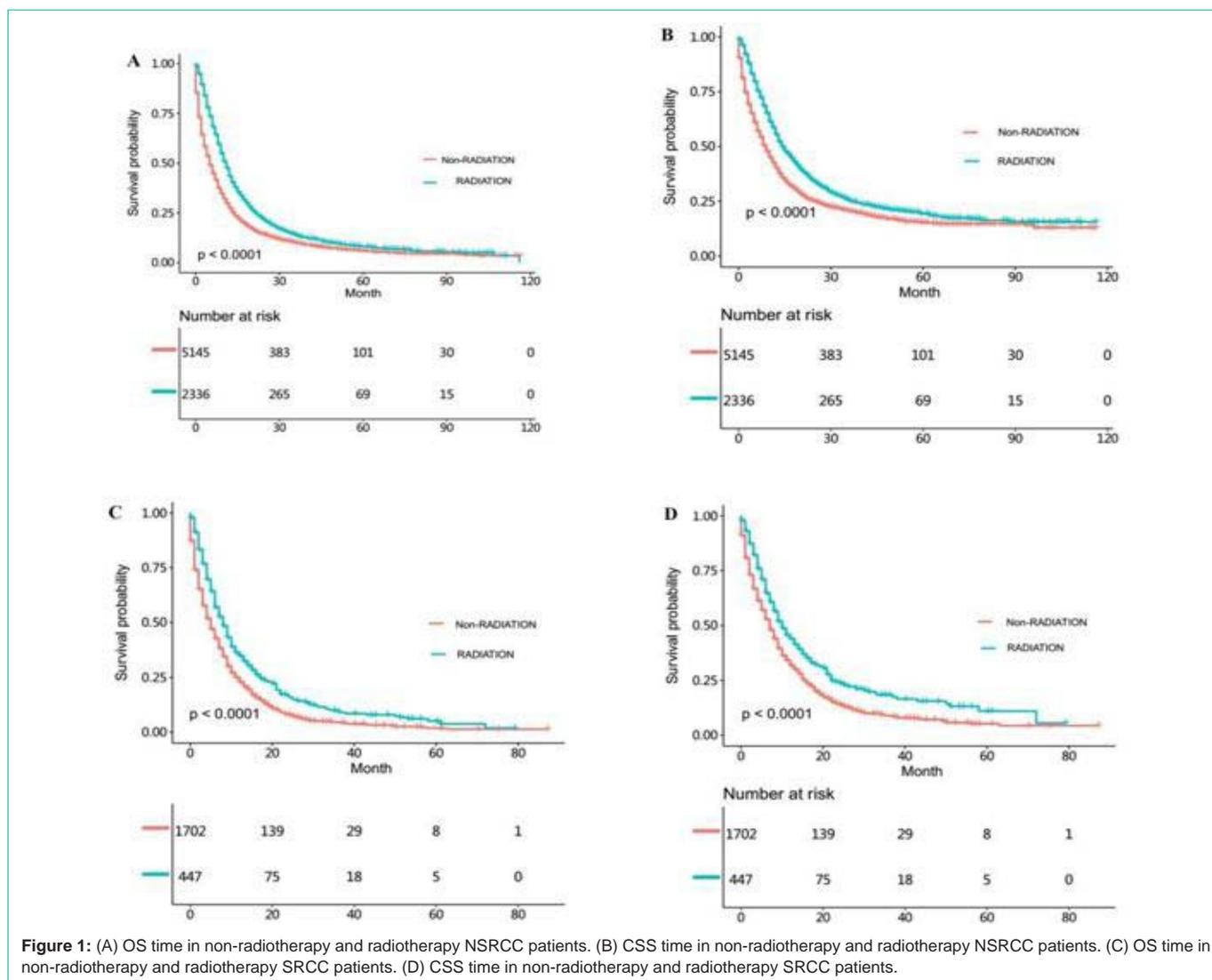
T2b	0.312(0.140-0.696)	0.004	0.881(0.391-1.984)	0.76	0.359(0.134-0.958)	0.041	1.010(0.374-2.725)	0.984
T3	0.416(0.186-0.928)	0.032	1.093(0.485-2.462)	0.83	0.474(0.177-1.265)	0.136	1.230(0.456-3.321)	0.683
T4	0.681(0.305-1.521)	0.349	1.170(0.520-2.633)	0.704	0.833(0.312-2.226)	0.716	1.346(0.499-3.628)	0.557
<b>N Stage (AJCC, 2004)</b>		<0.001				<0.001		
N0	Reference		Reference		Reference		Reference	
N1	1.206(1.126-1.293)	<0.001	1.270(1.179-1.368)	<0.001	1.318(1.216-1.428)	<0.001	1.325(1.215-1.445)	<0.001
N2	1.297(1.189-1.414)	<0.001	1.804(1.632-1.993)	<0.001	1.442(1.305-1.593)	<0.001	1.979(1.764-2.220)	<0.001
N3	1.708(1.531-1.905)	<0.001	2.103(1.863-2.373)	<0.001	2.010(1.779-2.272)	<0.001	2.405(2.100-2.755)	<0.001
<b>M Stage (AJCC, 2004)</b>		<0.001				<0.001		
M0	Reference		Reference		Reference		Reference	
M1	3.111(2.916-3.319)	<0.001	1.701(1.577-1.834)	<0.001	3.647(3.389-3.925)	<0.001	1.844(1.693-2.009)	<0.001
<b>Primary Site</b>		<0.001				<0.001		
Cardia	Reference		Reference		Reference		Reference	
Fundus of Stomach	0.961(0.805-1.146)	0.655	0.998(0.835-1.194)	0.985	1.035(0.849-1.261)	0.733	1.094(0.896-1.337)	0.378
Body of Stomach	0.899(0.804-1.004)	0.06	0.925(0.825-1.038)	0.184	0.913(0.804-1.038)	0.164	0.966(0.846-1.101)	0.602
Gastric Antrum	0.743(0.678-0.814)	<0.001	0.894(0.812-0.984)	0.022	0.718(0.645-0.798)	<0.001	0.896(0.801-1.002)	0.054
Pylorus	0.686(0.575-0.819)	<0.001	0.828(0.691-0.992)	0.041	0.687(0.559-0.844)	<0.001	0.869(0.704-1.072)	0.189
Lesser Curvature of Stomach	0.586(0.518-0.662)	<0.001	0.768(0.676-0.873)	<0.001	0.585(0.507-0.674)	<0.001	0.794(0.685-0.920)	0.002
Greater Curvature of Stomach	0.682(0.585-0.796)	<0.001	0.841(0.718-0.984)	0.031	0.706(0.592-0.843)	<0.001	0.893(0.746-1.070)	0.22
Overlapping Lesion of Stomach	1.173(1.055-1.304)	0.003	0.967(0.865-1.080)	0.549	1.238(1.097-1.396)	0.001	0.970(0.855-1.100)	0.635
Stomach	1.214(1.095-1.346)	<0.001	1.093(0.981-1.218)	0.107	1.222(1.085-1.376)	0.001	1.105(0.975-1.252)	0.117
<b>Tumor Size</b>		<0.001				<0.001		
≤1cm	Reference		Reference		Reference			
>1cm	2.116(1.993-2.247)	<0.001	1.301(1.215-1.394)	<0.001	2.294(2.14-2.459)	<0.001	1.352(1.249-1.464)	<0.001
<b>Gastrectomy</b>		<0.001				<0.001		
Yes	Reference		Reference		Reference		Reference	
No	3.405(3.194-3.629)	<0.001	2.758(2.536-2.998)	<0.001	3.598(3.344-3.872)	<0.001	2.942(2.671-3.240)	<0.001
<b>Radiation</b>		<0.001				<0.001		
Yes	Reference				Reference		Reference	
No	1.501(1.405-1.602)	<0.001	1.352(1.258-1.453)	<0.001	1.413(1.311-1.523)	<0.001	1.254(1.155-1.361)	<0.001

**Table 6:** Univariate and Multivariate Cox Analyses of NSRCC Patients According to Various Clinic pathological Variables.

Variable	Overall Survival				Cancer-Specific Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
<b>Gender</b>		0.251			<0.001			
Male	Reference		-		Reference	-	-	
Female	1.023(0.984-1.063)	0.251	-	-	1.041(0.994-1.091)	0.09		-
<b>Age</b>		<0.001			<0.001			
<65	Reference		Reference		Reference	-		
≥65	1.382(1.331-1.436)	<0.001	1.515(1.454-1.578)	<0.001	1.036(0.991-1.083)	0.123	-	-
<b>Insurance</b>		0.003			<0.001			
Uninsured	Reference		Reference		Reference			
Insured	1.146(1.036-1.267)	0.008	1.059(0.956-1.173)	0.274	1.260(1.121-1.416)	<0.001	1.078(0.958-1.213)	0.214
Unknown	1.051(1.011-1.093)	0.011	1.166(1.121-1.212)	<0.001	1.060(1.011-1.110)	0.015	1.196(1.140-1.254)	<0.001
<b>Tumor Grade</b>		<0.001				<0.001		

1	Reference		Reference		Reference		Reference	
2	1.439(1.312-1.577)	<0.001	1.258(1.146-1.380)	<0.001	1.664(1.470-1.884)	<0.001	1.344(1.186-1.523)	<0.001
3	1.887(1.726-2.064)	<0.001	1.549(1.414-1.698)	<0.001	2.451(2.172-2.766)	<0.001	1.775(1.569-2.007)	<0.001
4	1.702(1.446-2.005)	<0.001	1.481(1.255-1.746)	<0.001	2.196(1.792-2.691)	<0.001	1.693(1.379-2.078)	<0.001
<b>Race</b>		<0.001				<0.001		
Black	Reference		Reference		Reference		Reference	
Other	0.675(0.630-0.725)	<0.001	0.765(0.712-0.821)	<0.001	0.734(0.675-0.799)	<0.001	0.848(0.779-0.924)	<0.001
Unknown	0.512(0.326-0.804)	0.004	0.919(0.870-0.970)	0.002	0.884(0.830-0.943)	<0.001	0.926(0.866-0.990)	0.025
White	0.880(0.835-0.927)	<0.001	0.584(0.371-0.918)	0.02	0.610(0.366-1.015)	0.057	0.692(0.415-1.153)	0.158
<b>Marital Status</b>		<0.001				<0.001		
Divorced	Reference		Reference		Reference		Reference	
Married	0.832(0.777-0.890)	<0.001	0.853(0.796-0.913)	<0.001	0.803(0.741-0.870)	<0.001	0.829(0.764-0.899)	<0.001
Separated	0.859(0.710-1.039)	0.118	0.821(0.678-0.993)	0.043	0.879(0.703-1.100)	0.261	0.817(0.652-1.023)	0.077
Single	0.993(0.915-1.077)	0.864	0.966(0.890-1.048)	0.404	1.030(0.935-1.134)	0.551	0.968(0.879-1.066)	0.512
Widowed	1.212(1.124-1.308)	<0.001	1.090(1.009-1.178)	0.029	1.048(0.955-1.149)	0.322	1.073(0.976-1.179)	0.146
Other	0.987(0.882-1.106)	0.825	0.900(0.803-1.009)	0.071	0.905(0.788-1.040)	0.159	0.861(0.749-0.990)	0.036
<b>T Stage (AJCC, 2004)</b>		<0.001				<0.001		
T0	Reference		Reference		Reference		Reference	
T1	0.273(0.130-0.573)	0.001	0.534(0.254-1.124)	0.099	0.196(0.088-0.438)	<0.001	0.451(0.201-1.008)	0.052
T2a	0.193(0.092-0.406)	<0.001	0.498(0.236-1.050)	0.067	0.137(0.061-0.307)	<0.001	0.415(0.185-0.931)	0.033
T2b	0.263(0.125-0.553)	<0.001	0.608(0.289-1.280)	0.19	0.215(0.096-0.479)	<0.001	0.538(0.240-1.204)	0.131
T3	0.313(0.149-0.657)	0.002	0.710(0.337-1.496)	0.368	0.274(0.123-0.612)	0.002	0.664(0.297-1.487)	0.319
T4	0.595(0.283-1.250)	0.171	0.767(0.364-1.614)	0.484	0.538(0.241-1.200)	0.13	0.705(0.315-1.577)	0.395
<b>N Stage (AJCC, 2004)</b>		<0.001				<0.001		
N0	Reference		Reference		Reference		Reference	
N1	1.269(1.220-1.319)	<0.001	1.200(1.149-1.253)	<0.001	1.506(1.436-1.580)	<0.001	1.285(1.219-1.355)	<0.001
N2	1.375(1.293-1.463)	<0.001	1.694(1.582-1.813)	<0.001	1.719(1.599-1.848)	<0.001	1.882(1.738-2.039)	<0.001
N3	1.705(1.548-1.877)	<0.001	1.874(1.694-2.073)	<0.001	2.171(1.945-2.424)	<0.001	2.147(1.912-2.411)	<0.001
<b>M Stage (AJCC, 2004)</b>		<0.001				<0.001		
M0	Reference		Reference		Reference		Reference	
M1	3.007(2.890-3.128)	<0.001	1.658(1.582-1.737)	<0.001	3.717(3.548-3.893)	<0.001	1.900(1.797-2.008)	<0.001
<b>Primary Site</b>		<0.001				<0.001		
Cardia	Reference		Reference		Reference		Reference	
Fundus of Stomach	1.279(1.159-1.413)	<0.001	1.117(1.011-1.234)	0.03	1.201(1.063-1.357)	0.003	1.049(0.927-1.186)	0.449
Body of Stomach	1.093(1.017-1.176)	0.016	1.044(0.968-1.125)	0.264	1.022(0.934-1.118)	0.641	0.998(0.910-1.095)	0.966
Gastric Antrum	0.975(0.926-1.026)	0.329	1.013(0.959-1.071)	0.637	0.916(0.861-0.976)	0.006	0.993(0.928-1.064)	0.851
Pylorus	0.987(0.889-1.096)	0.808	1.102(0.990-1.226)	0.075	1.006(0.889-1.139)	0.921	1.167(1.027-1.326)	0.017
Lesser Curvature of Stomach	0.833(0.776-0.895)	<0.001	0.869(0.807-0.937)	<0.001	0.765(0.699-0.836)	<0.001	0.823(0.750-0.904)	<0.001
Greater Curvature of Stomach	1.087(0.986-1.190)	0.095	1.186(1.073-1.310)	0.001	1.020(0.904-1.151)	0.747	1.144(1.011-1.294)	0.033
Overlapping Lesion of Stomach	1.478(1.369-1.596)	<0.001	1.166(1.077-1.263)	<0.001	1.570(1.435-1.717)	<0.001	1.199(1.093-1.315)	<0.001
Stomach	1.339(1.257-1.425)	<0.001	1.110(1.040-1.186)	0.002	1.249(1.156-1.349)	<0.001	1.047(0.965-1.135)	0.268
<b>Tumor Size</b>		<0.001				<0.001		
≤1cm	Reference		Reference		Reference			
>1cm	1.876(1.809-1.946)	<0.001	1.151(1.105-1.200)	<0.001	1.970(1.885-2.060)	<0.001	1.170(1.113-1.230)	<0.001
<b>Gastrectomy</b>		<0.001				<0.001		

Yes	Reference		Reference		Reference		Reference	
No	3.294(3.172-3.420)	<0.001	2.780(2.648-2.918)	<0.001	3.514(3.358-3.678)	<0.001	2.834(2.671-3.008)	<0.001
<b>Radiation</b>		<0.001				<0.001		
Yes	Reference				Reference		Reference	
No	1.356(1.304-1.410)	<0.001	1.405(1.347-1.466)	<0.001	1.250(1.193-1.309)	<0.001	1.326(1.260-1.395)	<0.001

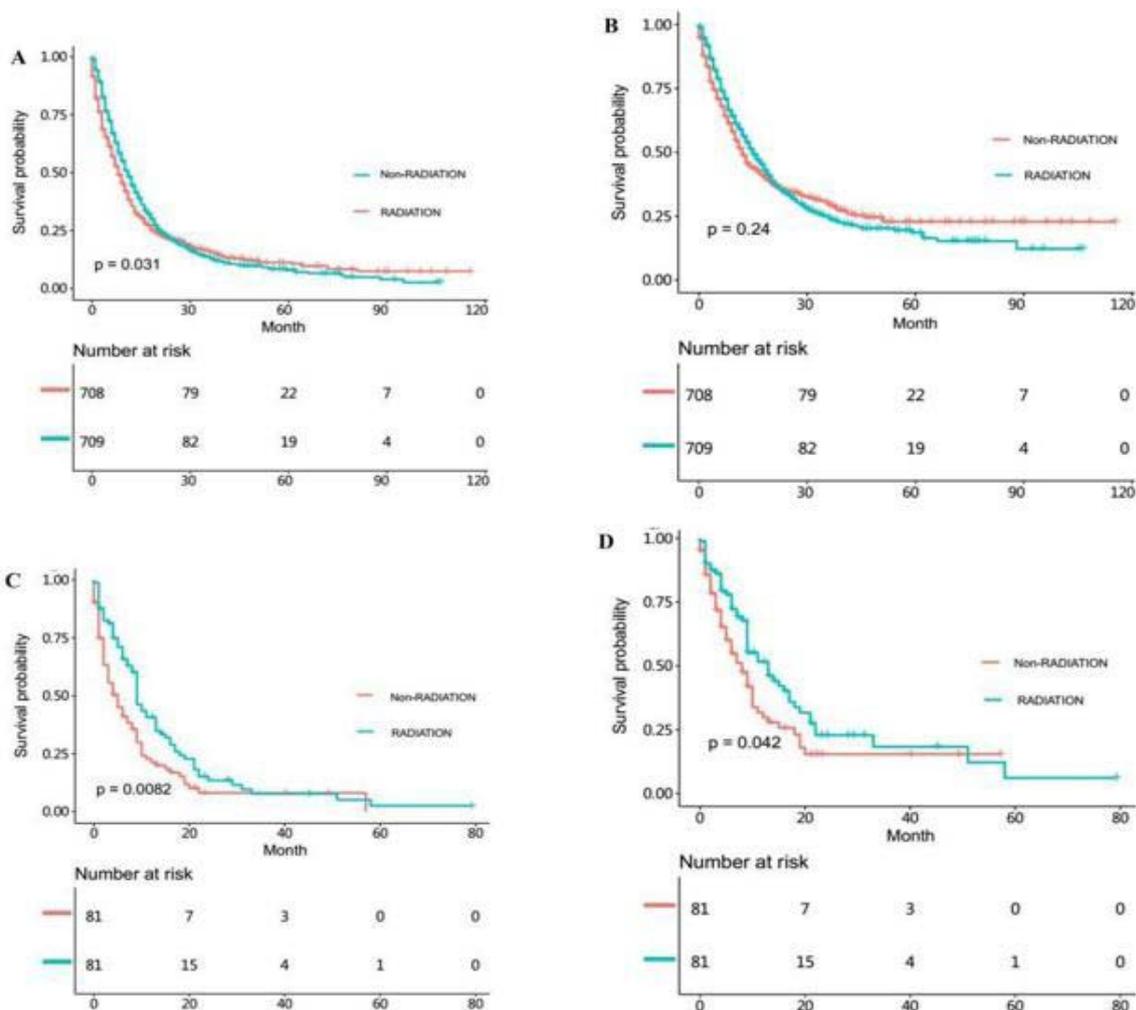


**Figure 1:** (A) OS time in non-radiotherapy and radiotherapy NSRCC patients. (B) CSS time in non-radiotherapy and radiotherapy NSRCC patients. (C) OS time in non-radiotherapy and radiotherapy SRCC patients. (D) CSS time in non-radiotherapy and radiotherapy SRCC patients.

**The influence of radiotherapy on survival time of SRCC and NSRCC patients**

In order to further investigate the differences between the effects of radiotherapy on the survival time of SRCC and NSRCC patients, we divided the SRCC and NSRCC patients who were not undergoing gastrectomy into non-radiotherapy NSRCC group, radiotherapy NSRCC group, non-radiotherapy SRCC group and radiotherapy SRCC group (Table 1 and 2). In Figure 1A-1D, we mainly compared the effects of radiotherapy in non-operative SRCC and NSRCC patients groups. The differences of OS (HR=0.663, 95% CI=0.635-0.691, p<0.001) and CSS (HR=0.668, 95% CI=0.636-0.702, p<0.001) time between non-radiotherapy and radiotherapy NSRCC group were

compared. The results showed that the prognosis of radiotherapy NSRCC group was significantly better than non-radiotherapy NSRCC group (Figure 1A and 1B). In addition, we compared the difference of OS (HR=0.691, 95% CI=0.629-0.758, p<0.001) and CSS (HR=0.710, 95% CI=0.638-0.789, p<0.001) time between non-radiotherapy and radiotherapy SRCC group, which showed that the prognosis of radiotherapy SRCC group was better than non-radiotherapy SRCC group. Based on the above results, we can learn that radiotherapy benefits the prognosis of both SRCC and NSRCC patients. In order to eliminate the effects of other factors, we re-compared the OS and CSS time of the non-radiotherapy and radiotherapy NSRCC group through PSM. In Figure 2A, 2B and 3, we compared the OS and



**Figure 2:** (A) OS time in non-radiotherapy and radiotherapy NSRCC patients after PSM analysis. (B) CSS time in non-radiotherapy and radiotherapy NSRCC patients after PSM analysis. (C) OS time in non-radiotherapy and radiotherapy SRCC patients after PSM analysis. (D) CSS time in non-radiotherapy and radiotherapy SRCC patients after PSM analysis.

CSS time after PSM in non-radiotherapy and radiotherapy NSRCC group. According to results reflected in Figure 2A, the OS time in radiotherapy NSRCC group was better than in non-radiotherapy NSRCC group (HR=0.882, 95% CI=0.785-0.992, P=0.037), but the lifetime curves was intersected. We then segmented the statistical data and the results showed that the OS time in two groups had no statistical difference (Figure 3). And there was no statistical difference in the CSS time between radiotherapy and non-radiotherapy NSRCC group (HR=0.921, 95% CI=0.800-1.060, p=0.252) (Figure 2B). Next, we also compared the OS and CSS time after PSM in non-radiotherapy and radiotherapy SRCC group, and the OS (HR=0.649, 95% CI=0.462-0.910, p=0.012) and CSS (HR=0.674, 95% CI=0.453-0.901, p=0.042) time in radiotherapy SRCC group were better than that in non-radiotherapy SRCC group. From the above data, we can initially get the conclusion that radiotherapy for SRCC patients may be more effective than NSRCC patients, with statistical differences.

**The influence of radiotherapy and gastrectomy on survival time in SRCC and NSRCC patients**

For patients undergoing gastrectomy, they were also divided into

non-radiotherapy NSRCC group, radiotherapy NSRCC group, non-radiotherapy SRCC group and radiotherapy SRCC group (Table 3 and 4). In Figure 4A-4D and Figure 5 and 6, we mainly compared the effects of radiotherapy on the SRCC and NSRCC patients with gastrectomy. As reflected in Figure 4A, the OS time in radiotherapy NSRCC group is better than that in non-radiotherapy NSRCC group (HR= 0.771, 95% CI=0.729-0.816, p<0.0001). And the CSS time in radiotherapy NSRCC group was better than that in non-radiotherapy NSRCC group (HR=0.915, 95% CI=0.855-0.979, p=0.01), but the lifetime curves was also intersected (Figure 4B). We then segmented the statistical analysis data and the results showed that the CSS time in radiotherapy NSRCC group was better than that in non-radiotherapy NSRCC group during the first two years, but after the period time the CSS time in non-radiotherapy NSRCC group was better than that in radiotherapy NSRCC group.

We next compared the OS time in non-radiotherapy and radiotherapy SRCC groups, the results demonstrated that OS time in radiotherapy SRCC group was better than that in non-radiotherapy SRCC group (HR=0.792, 95% CI=0.730-0.860, p<0.0001) (Figure 4C).

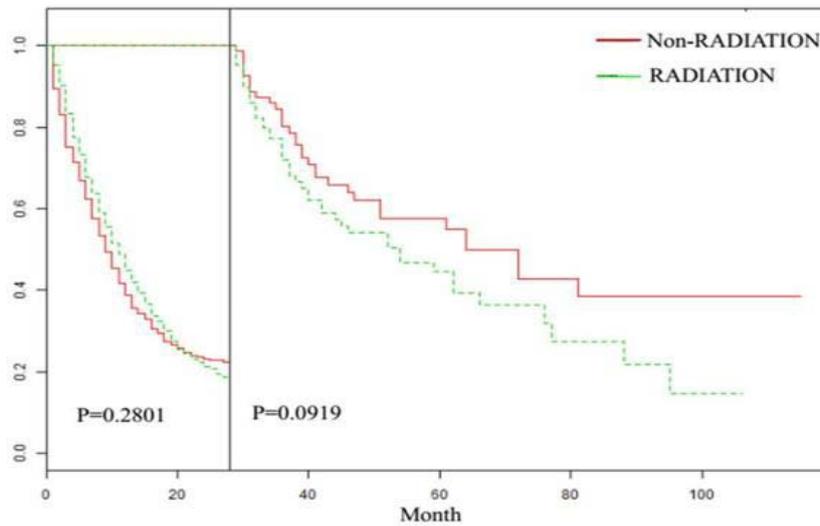


Figure 3: Landmark Estimation of OS time in non-radiotherapy and radiotherapy NSRCC patients after PSM analysis.

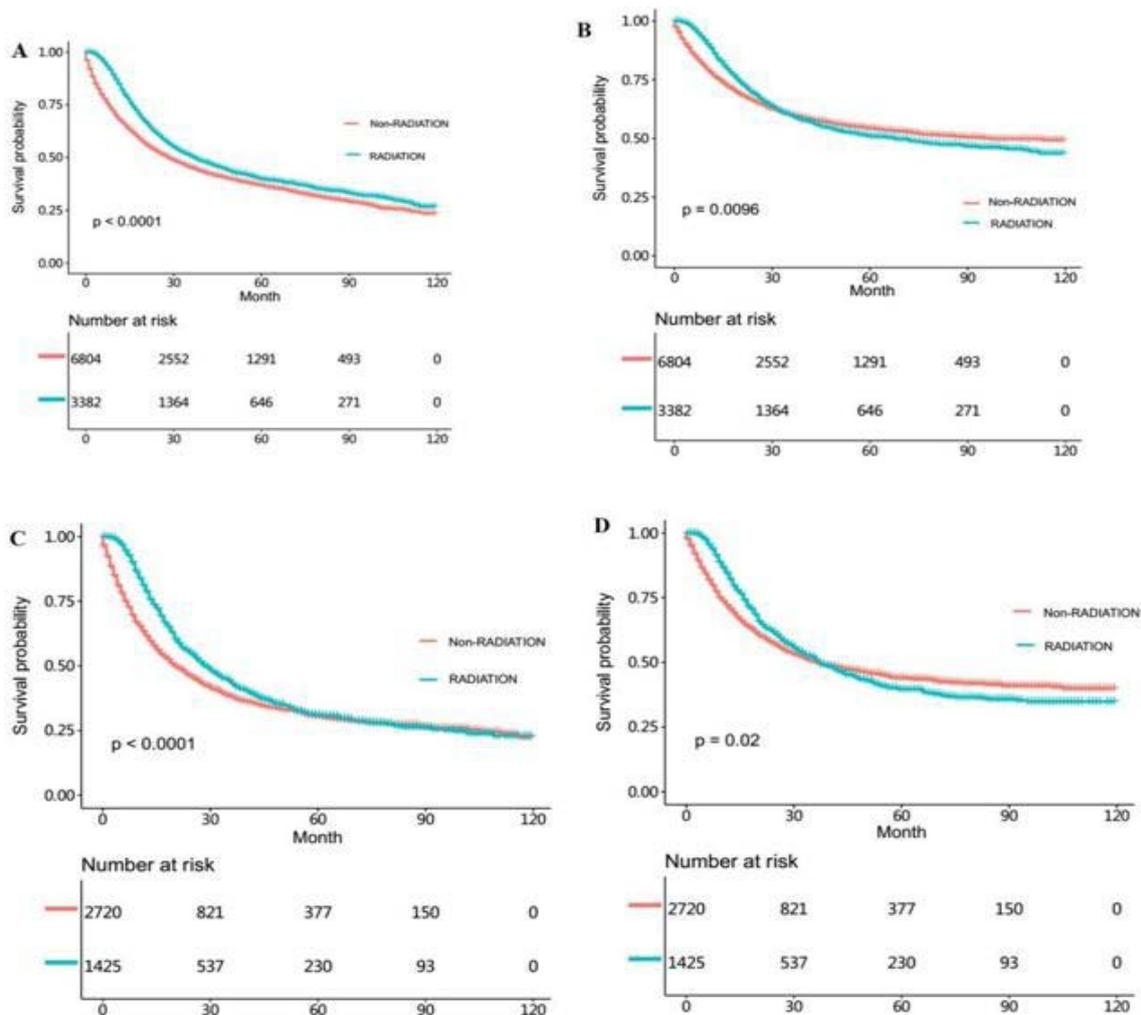


Figure 4: (A) OS time in non-radiotherapy and radiotherapy NSRCC patients under gastrectomy treatment. (B) CSS time in non-radiotherapy and radiotherapy NSRCC patients undergoing gastrectomy treatment. (C) OS time in non-radiotherapy and radiotherapy SRCC patients under gastrectomy treatment. (D) CSS time in non-radiotherapy and radiotherapy SRCC patients under gastrectomy treatment.

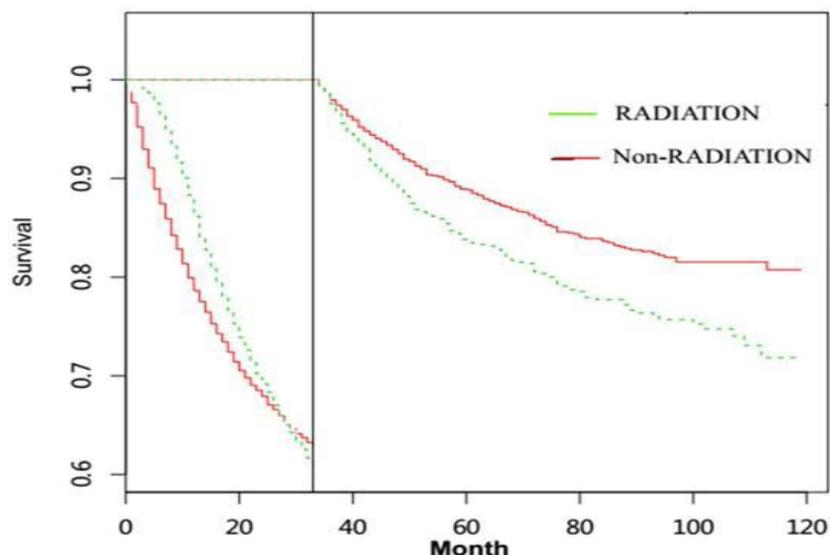


Figure 5: Landmark Estimation of CSS time in non-radiotherapy and radiotherapy NSRCC patients under gastrectomy treatment.

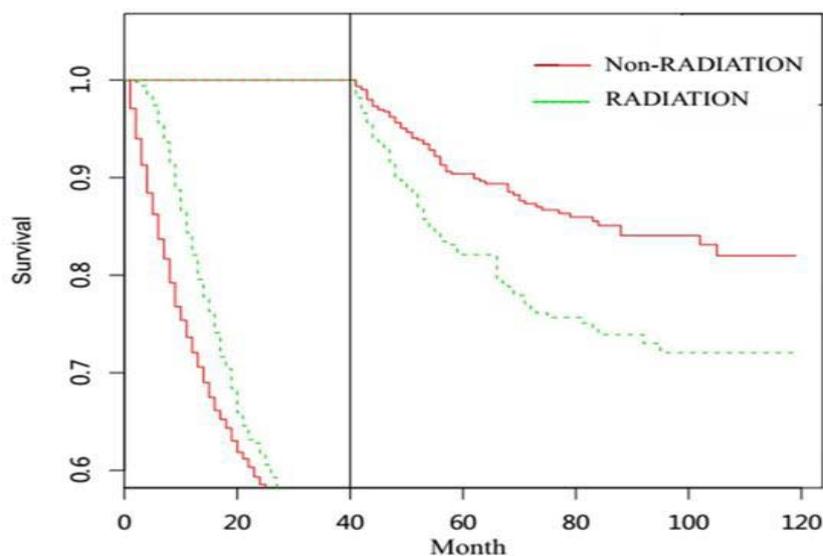


Figure 6: Landmark Estimation of CSS time in non-radiotherapy and radiotherapy SRCC patients under gastrectomy treatment.

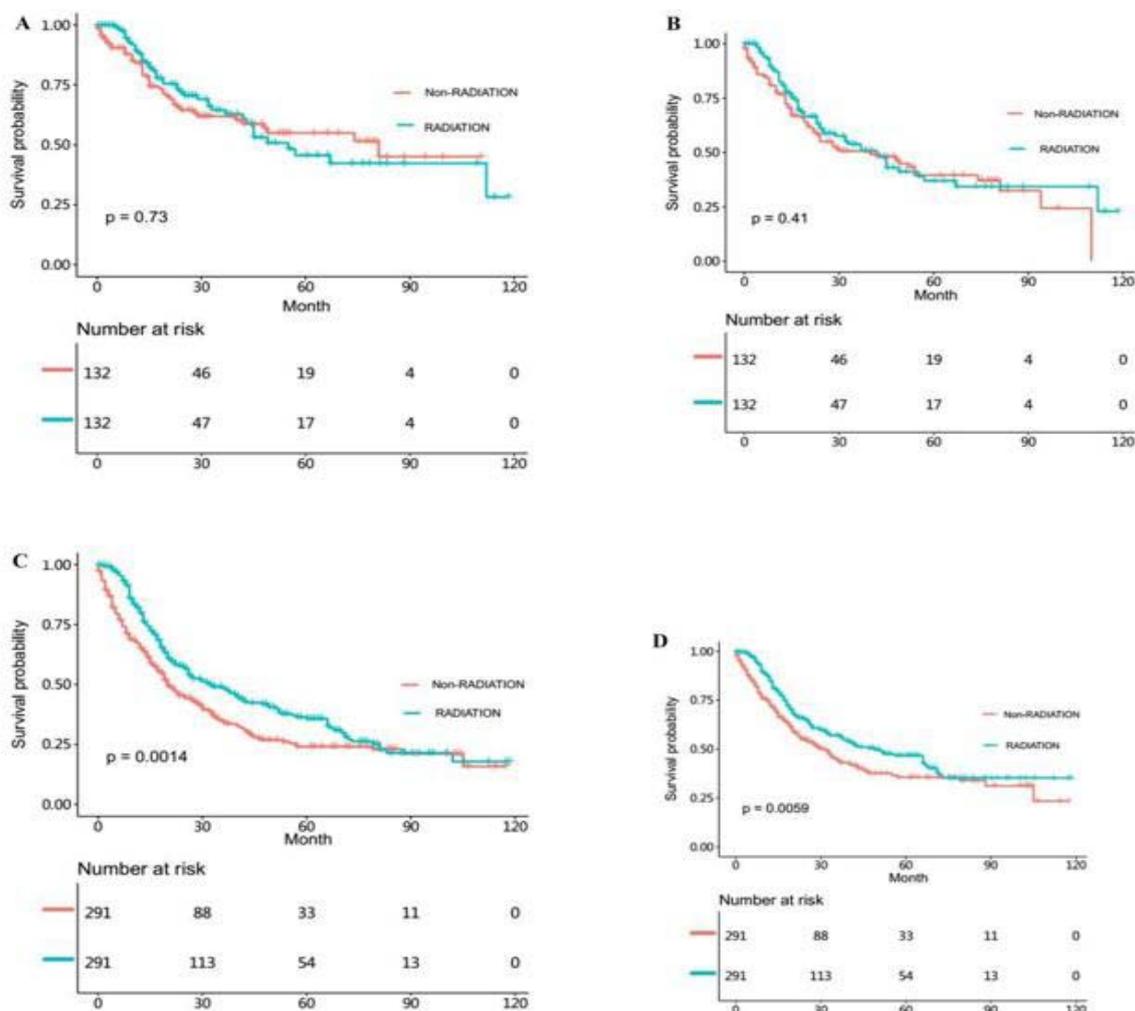
As shown in Figure 4D, the CSS time in radiotherapy SRCC group was also better than in non-radiotherapy SRCC group (HR=0.895, 95% CI=0.814-0.984, p=0.021), but the lifetime curves were intersected. We then segmented the statistical analysis data and the result indicated that during the first 40 months the CSS time in radiotherapy SRCC group was better than that in non-radiotherapy SRCC group, but after that period time, the CSS in non-radiotherapy SRCC group was better than that in radiotherapy SRCC group which had statistical difference (Figure 6). By comparing the survival time of these groups, we could conclude that radiotherapy did not benefit all patients, especially for those undergoing gastrectomy.

In order to eliminate the imbalanced factors of the two groups we further analyzed the data by PSM method. The OS and CSS time of the matched non-radiotherapy and radiotherapy NSRCC groups were

then compared. From the results, we could learn that there was no significant statistical differences in OS (HR =0.939, 95% CI=0.698-1.263, p=0.730) and CSS (HR=0.866, 95% CI =0.604-1.240, p=0.410) time between the non-radiotherapy and radiotherapy NSRCC groups (Figure 7A and 7B). And we also compared the OS and CSS time in the non-radiotherapy and radiotherapy SRCC group and the results demonstrated that the OS (HR=0.719, 95% CI=0.584-0.883, p=0.0014) and CSS (HR=0.718, 95% CI =0.566-0.912, p=0.0059) time in the radiotherapy SRCC group were both better than those in the non-radiotherapy SRCC group.

### Discussion

Based on the analysis data obtained from SEER database, we discuss the clinical value of radiotherapy in SRCC and NSRCC patients in this study. Through the multivariate analysis and



**Figure 7:** (A) OS time in non-radiotherapy and radiotherapy NSRCC patients under gastrectomy treatment after PSM analysis. (B) CSS time in non-radiotherapy and radiotherapy NSRCC patients undergoing gastrectomy treatment after PSM analysis. (C) OS time in non-radiotherapy and radiotherapy SRCC patients under gastrectomy treatment after PSM analysis. (D) CSS time in non-radiotherapy and radiotherapy SRCC patients under gastrectomy treatment after PSM analysis.

univariate analysis strategies, we found that radiotherapy is of obvious value to both SRCC and NSRCC patients. However, the effect of radiotherapy on the prognosis of SRCC patients was better than that in NSRCC patients by using univariate analysis. In order to study the reasons for the differences, we divided the patient into different groups based on whether they received gastrectomy. According to the OS and CSS time, we could learn that radiotherapy had benefits on non-gastrectomy SRCC group and NSRCC group patients. In order to eliminate the multivariate factors, we then compared the groups with PSM matching method. The radiotherapy had no effect on the OS and CSS in NSRCC group, while radiotherapy had obvious benefit for SRCC group. Next, we studied the effects of gastrectomy combined with radiotherapy on SRCC group and NSRCC group patients and we have found that the OS time was significantly improved in SRCC group and NSRCC group under gastrectomy and radiotherapy treatment. However, the effect in SRCC group and NSRCC group was reversed after a period time of 40 months and 32 months, respectively. So we further compared them with PSM. Data showed that radiotherapy had no effect on the OS and CSS time in NSRCC

group, while radiotherapy had obvious benefits for SRCC group. In this study, we got the conclusion that SRCC patients were more sensitive to radiotherapy than NSRCC patients were, which had never been reported before.

For early-stage gastric cancer patients, gastrectomy is the main treatment to achieve the goal of R0 resection and the surgical margin less than 4cm. But the role of radiotherapy in the treatment of gastric cancer patients is still controversial. Then two randomized trials compared the effects of surgery together with radiotherapy or chemotherapy were conducted in the premise that gastric cancer patients received resection. A gastric cancer study group in the UK randomly divided patients into gastrectomy or gastrectomy combined with radiotherapy groups, although there was a significant reduction in the recurrence of local lesions in patients undergoing radiotherapy, no survival benefits were found [16]. Zhang [17] divided the patients into preoperative radiotherapy treatment and surgery alone groups and reported that radiotherapy could improve survival rates and surgical resection rates. A recent meta-analysis assessed the role of preoperative, postoperative and intraoperative

radiotherapy in resectable gastric carcinoma patients and results showed that patients undergoing radiotherapy had significantly improved OS time in 5 years [18]. Through Cox regression analysis in our study, it could be found that radiotherapy has benefited both the SRCC and NSRCC group patients, but according to the classification treatment and survival time comparison, we found that radiotherapy benefits for NSRCC patients seem inferior to SRCC patients. The benefits of radiotherapy for the SRCC group are certain and no similar studies have been carried out in the relevant literature. However, the molecular biological differences between the two groups remained unclear.

SRCC is a more common type of gastric adenocarcinoma with more than 50% of tumor cells are rich in intracellular mucus. Through this study, it can be found that there were many obvious differences in clinic pathological features of SRCC and NSRCC patients. For example, SRCC patients are mostly women, have younger age, lower tumor differentiation and higher incidence of lymphatic and distant metastasis [19]. These characteristics of SRCC patients might be the reasons of making their prognosis significantly lower than NSRCC patients. Compared to the formation process of NSRCC, SRCC mainly has two pathological processes of cell adhesion molecules loss and accumulations of mucus into large vacuoles in the cellular level. E-cadherin protein encoded by CDH1 gene is a cell-cell adhesion molecule, which plays a key role in tumor progression and epithelial mesenchymal transformation. And the increased E-cadherin protein expression is an important reason for the occurrence of SRCC [20]. Moreover, E-cadherin is a key component of epithelial cell adhesion connections and is necessary for the normal formation and maintenance of epithelial cells [21]. E-cadherin protein reduction is an important factor leading to the invasion and metastasis of epithelial tumors [22]. During the course of tumor progression, various mechanisms might lead to decreased E-cadherin level, which leads to the destruction of normal cell adhesion and enhances the movement and invasion of tumor cells [23]. E-cadherin expression is also closely related to the degree of differentiation in gastric cancers. Almost all the relevant studies showed that the expression level of E-cadherin in gastric cancer tissue with well differentiation was significantly higher than that with poor differentiation or no differentiation. Karayiannakis's [24] study of 83 gastric cancer cases showed that the abnormal expression of E-cadherin in adenocarcinoma was 57%, while the abnormal expression level in ring cell carcinoma and undifferentiated carcinoma were 84% and 87%, respectively. This may be an important reason for the poor differentiation and distant metastasis of SRCC. Ray's [25] study on radiotherapy sensitivity through comparing E-cadherin expression in prostate cancer patients found that the decline in E-cadherin expression was associated with a decreased sensitivity to radiotherapy, suggesting that E-cadherin expression could promote the treatment effect of radiotherapy in prostate cancer patients, which mainly illustrates the role of E-cadherin expression in radiotherapy sensitivity, but the specific mechanism has not been further studied.

Our study incorporates a large number of patients from multi-center population data in United States, avoiding related bias caused by a single agency experience or a limited sample size. But due to the non-stochastic nature of SEER, some limitations of current research are worth discussing. First, it is not feasible to

review individual pathological diagnoses in large populations and interpretation differences between pathologists may lead to incorrect classification. Second, the SEER registration form does not include detailed information on the dose of radiotherapy and chemotherapy, including PRT or the durations of radiotherapy and chemotherapy. Therefore, we are unable to take the differences in radiotherapy treatment into account during the study period. Although there is no data on cancer recurrence in this study, CSS is a reasonable index to evaluate the prognosis of gastric cancer patients. The results of the current study may provide some scientific information for future research on the specific effect of radiotherapy on SRCC patients. In order to get a more explicit conclusion, we will conduct a larger randomized and controlled trial of the Chinese population through multi-center cooperation method.

To sum up, our results show that compared to NSRCC, SRCC is a unique type of gastric cancer, which is more likely to affect younger patients, have features such as manifested in more advanced tumors and less differentiated in diagnosis. The sensitivity of SRCC to radiotherapy is higher than NSRCC patients. Although the prognosis of SRCC patients is far less than that of NSRCC patients, the treatment strategy of surgical resection of primary lesions combined with radiotherapy should be recommended for SRCC patients. And whether radiotherapy benefits NSRCC patients still needs further to be explored.

## Availability of Data and Materials

In this study, the clinical value of radiotherapy for SRCC and NSRCC patients using SEER database (<http://seer.cancer.gov/about/overview.html>), which is maintained by the National Cancer Institute and includes 18 population-based cancer registries with information of cancer morbidity and mortality in the United States.

Lei Yu conceived and designed the study; Chunming Wang, Huafu Li and Jianwu Luo performed the data statistics; Huafu Li and Riqiang Liu wrote the paper. All authors read and approved the final manuscript.

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