



Survival comparison of stage IIA rectal cancer with or without neoadjuvant therapy: a SEER database analysis with propensity score matching

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Background: Patients with stage IIA rectal cancer have a higher survival rate but side effects from chemoradiotherapy; thus, whether neoadjuvant therapy should be performed for stage IIA rectal cancer is controversial. This study aimed to compare the survival outcomes of patients with stage IIA rectal cancer with or without neoadjuvant chemoradiotherapy.

Methods: Patients with stage IIA rectal cancer between 2010 and 2015 were included through the Surveillance, Epidemiology, and End Results database. Propensity score matching was used to reduce the impact of confounding factors. Survival curves were plotted using the Kaplan-Meier method, and survival differences were assessed using the log-rank test.

Results: There were no significant differences in overall survival and cancer-specific survival between the neoadjuvant chemoradiotherapy and surgery groups ($P=0.973$ and 0.983). Compared with the surgery group, the neoadjuvant chemoradiotherapy + surgery + chemotherapy group had a better overall survival ($P=0.007$). Subgroup analysis showed that the neoadjuvant chemoradiotherapy + surgery + chemotherapy group had better overall survival compared to the surgery group in the subgroup containing preoperative high-risk factors ($P=0.003$) but not in the low-risk subgroup ($P=0.685$).

Conclusions: There is no evidence that neoadjuvant chemoradiotherapy + surgery can improve overall survival and cancer-specific survival compared to surgery alone in patients with stage IIA rectal cancer. Neoadjuvant chemoradiotherapy + surgery + chemotherapy can improve overall survival compared to surgery alone, but only in patients with preoperative high-risk factors. We suggest that patients with no preoperative high-risk factors may be considered for surgery alone, neoadjuvant chemoradiotherapy + surgery + chemotherapy is recommended for patients with preoperative risk factors.

Keywords: Stage IIA; rectal cancer; neoadjuvant therapy; Surveillance, Epidemiology, and End Results database (SEER database); propensity score matching (PSM)

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Introduction

Colorectal cancer is one of the most common malignancies in the world, with the third-highest incidence and death rate among all malignancies (1,2). Rectal cancer accounts for approximately 30% of all colorectal cancer cases (1). The treatment has evolved with the introduction of neoadjuvant radiotherapy and chemotherapy before total mesorectal resection (TME) surgery (3). Currently, neoadjuvant chemoradiotherapy (CRT), TME, and adjuvant chemotherapy are the primary recommended treatments for patients with locally advanced rectal cancer (LARC) (4). Among them, neoadjuvant CRT has been widely accepted as a therapeutic method to reduce tumor stage, increase resectability, and reduce the local recurrence rate of patients with LARC (5). However, this success in improving survival comes at the cost of a significant reduction in quality of life (6). The National Comprehensive Cancer Network (NCCN) Guidelines recommend neoadjuvant and adjuvant therapy for patients at high risk of local recurrence, including stage II (T3–4, N0, tumor invasion of the myenteric layer or further) and stage III (N+, no distant metastases) (7). The European Society of Medical Oncology (ESMO) guidelines first recommended in 2013 that the treatment of rectal cancer should be stratified according to the risk of recurrence. For patients with low-risk rectal cancer, including early T3N0, and no significant invasion of the vasculature or rectal mesentery, surgical treatment can be considered directly (8). In addition, some studies have indicated that neoadjuvant CRT only reduces the risk of local recurrence but not distant metastasis (9), and fails to improve long-term survival and retention of the anal sphincter (10). Therefore, the need to complete neoadjuvant CRT for patients with different stages of LARC, such as stage IIA (T3N0M0), has generated some new controversies in different guidelines and literature.

Hence, our primary objective was to investigate the impact of neoadjuvant CRT on the prognosis of patients with stage IIA rectal cancer and to explore whether neoadjuvant CRT is necessary for these patients. Here, we performed an analysis comparing survival and clinicopathological differences between patients with stage IIA rectal cancer who underwent surgery alone and those who completed neoadjuvant CRT, applying a propensity score matching (PSM) method based on the information in the U.S. Surveillance, Epidemiology, and End Results (SEER) database. We present the following article in accordance with the STROBE reporting checklist (available

at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-166/rc>).

Methods

Patient selection

The SEER database comprises 18 cancer registries covering 27.8% of the U.S. population and collects and provides data on cancer clinicopathology, morbidity, and survival data. We extracted demographic and clinicopathological data of patients diagnosed with rectal cancer between January 2010 and December 2015 from the SEER database [database name: Incidence-SEER Research (Plus) Data, 18 Registries, Nov 2020 Sub (2000–2018)]. Patients who met the following criteria were included: (I) clear pathological diagnosis of rectal malignant tumors; (II) diagnosis time was from January 2010 to December 2015; (III) the American Joint Committee on Cancer (AJCC) stage was IIA; (IV) surgery has been completed definitely; (V) neoadjuvant therapy has been specified in the CRT database; and (VI) known time of survival and cause of death. Patients with the following criteria were excluded: (I) borderline tumors of the rectum; (II) local tumor resection only; (III) neoadjuvant therapy is not clear in the CRT database; (IV) colorectal cancer diagnosed by death certificate or autopsy; (V) other concurrent or multiple malignant tumors.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since the data of this project were all extracted from the SEER database and did not involve patient safety, privacy, and postoperative follow-up, no informed consent and no ethics committee approval were required.

Result measurement

Information on the following clinicopathological variables was extracted from the SEER database: sex, age, year of diagnosis, race, site of lesion, type of pathology, histological grade, TNM stage according to AJCC, number of lymph nodes harvested intraoperatively (LNH), whether radiotherapy or chemotherapy was administered and in sequence with surgery, carcinoembryonic antigen (CEA), tumor deposits (TD), perineural invasion (PNI), tumor size, follow-up time, tumor-specific deaths, and deaths from other causes. The primary outcomes were overall survival (OS) and cancer-specific survival (CSS). OS was defined as the time from diagnosis to death from any cause. CSS was

defined as the time from diagnosis to cancer-specific death, with the data on death from other causes or survival at the end of follow-up being censored.

Statistical analysis

A logistic regression model was applied for PSM (3:1 matching), with a matching tolerance of 0.02 and without replacement. Survival curves were plotted using the Kaplan-Meier method, survival differences were assessed using the log-rank test, and multivariate analysis was performed using the Cox proportional risk model to generate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$ for a two-tailed test. All statistical analyses were performed using IBM SPSS Statistics 26.0 and R 4.1.0. All survival curves were plotted using GraphPad Prism 8.2.1.

Results

We screened and analyzed 14,505 patients with stage IIA rectal cancer from the database. Among them, 8,708 patients underwent surgery only, and 5,797 underwent perioperative therapy, including neoadjuvant and/or adjuvant therapy. When cases with incomplete data have been excluded, 3,976 patients underwent surgery alone, 1,055 patients underwent neoadjuvant CRT + surgery, 547 patients underwent neoadjuvant CRT + surgery + adjuvant chemotherapy, and 276 patients underwent surgery + adjuvant chemotherapy. Of these patients, the median follow-up time was 58 months (interquartile range, 41–78 months). A total of 1,675 (28.6%) patients died at the end of follow-up, and 939 patients (16.0%) died specifically from rectal cancer.

Confounding factors including age, sex, race, grade, LNH, TD, CEA, PNI and tumor size were adjusted. Before PSM, the surgery group had older patients ($P = 0.02$), and more LNH ($P < 0.01$) compared to the neoadjuvant CRT + surgery group. After PSM, 1,055 matched pairs were created, and the distributions of variables were balanced (Table 1). Before PSM, the surgery group had more female ($P = 0.02$), older patients ($P < 0.01$), more LNH ($P < 0.01$), and more larger tumors ($P = 0.01$) compared to the neoadjuvant CRT + surgery + chemotherapy group. After PSM, 547 matched pairs were created, and the distributions of variables were balanced (Table 2). Before PSM, the surgery + chemotherapy group had more female ($P < 0.01$), higher

grade ($P < 0.01$), more LNH ($P < 0.01$), and more larger tumors ($P = 0.01$) compared to the neoadjuvant CRT + surgery + chemotherapy group. After PSM, 237 matched pairs were created, and the distributions of variables were balanced (Table 3).

Neoadjuvant CRT + surgery vs. surgery alone

After PSM, the Kaplan-Meier analysis showed that there was no statistically significant difference in OS between patients who underwent neoadjuvant CRT + surgery and those who underwent surgery alone ($P = 0.973$) (Figure 1A), and the 5-year OS were 75.9% (95% CI: 73.0–78.5%) and 74.5% (95% CI: 72.8–76.1%) respectively. The Kaplan-Meier analysis showed that there was no statistically significant difference in CSS between these two groups as well after PSM ($P = 0.983$) (Figure 1B), and the 5-year CSS were 85.2% (95% CI: 82.7–87.4%) and 84.5% (95% CI: 83.0–85.9%) respectively.

Neoadjuvant CRT + surgery + chemotherapy vs. surgery alone

After PSM, the Kaplan-Meier analysis showed that patients with stage IIA rectal cancer treated with neoadjuvant CRT + surgery + chemotherapy had better OS than those treated with surgery alone ($P = 0.007$) (Figure 2A) and the 5-year OS were 81.6% (95% CI: 77.7–84.9%) and 76.3% (95% CI: 74.0–78.5%) respectively. The Kaplan-Meier analysis showed that there was no statistically significant difference in CSS between these two groups ($P = 0.267$) (Figure 2B). The 5-year CSS were 86.2% (95% CI: 82.6–89.1%) and 84.9% (95% CI: 82.8–86.7%) respectively.

Neoadjuvant CRT + surgery + chemotherapy vs. surgery + chemotherapy

After PSM, the Kaplan-Meier analysis showed that patients with stage IIA rectal cancer treated with neoadjuvant CRT + surgery + chemotherapy had better OS than those treated with surgery + chemotherapy, but the difference was not statistically significant ($P = 0.114$) (Figure 3A), and the 5-year OS were 83.4% (95% CI: 78.5–87.3%) and 80.8% (95% CI: 74.7–85.6%) respectively. The Kaplan-Meier analysis showed that there was no statistically significant difference in CSS between these two groups ($P = 0.270$) (Figure 3B). The 5-year CSS were 86.7% (95% CI: 82.1–90.2%) and

Table 1 Demographic and clinicopathologic data for surgery only group and neoadjuvant chemoradiotherapy + surgery group before and after PSM

Variables	Before PSM				After PSM			
	No. of patients	Surgery only	Neoadjuvant CRT + surgery	P value	No. of patients	Surgery only	Neoadjuvant CRT + surgery	P value
No. of patients	5,031	3,976	1,055	–	4,041	2,986	1,055	–
Sex, n (%)				0.23				0.83
Male	3,088	2,423 (60.9)	665 (63.0)		2,534	1,869 (62.6)	665 (63.0)	
Female	1,943	1,553 (39.1)	390 (37.0)		1,507	1,117 (37.4)	390 (37.0)	
Age, n (%)				0.02				0.72
<55 years	1,250	970 (24.4)	280 (26.5)		1,048	768 (25.7)	280 (26.5)	
55–64 years	1,376	1,065 (26.8)	311 (29.5)		1,173	862 (28.9)	311 (29.5)	
≥65 years	2,405	1,941 (48.8)	464 (44.0)		1,820	1,356 (45.4)	464 (44.0)	
Race, n (%)				0.72				0.81
White	4,057	3,197 (80.4)	860 (81.5)		3,319	2,459 (82.4)	860 (81.5)	
Black	406	324 (8.1)	82 (7.8)		299	217 (7.3)	82 (7.8)	
Other	568	455 (11.4)	113 (10.7)		423	310 (10.4)	113 (10.7)	
Grade, n (%)				0.55				0.90
I & II	4,576	3,611 (90.8)	965 (91.5)		3,702	2,737 (91.7)	965 (91.5)	
III & IV	455	365 (9.2)	90 (8.5)		339	249 (8.3)	90 (8.5)	
LNH, n (%)				<0.01				0.06
<12	1,396	1,022 (25.7)	374 (35.5)		1,335	961 (32.2)	374 (35.5)	
≥12	3,635	2,954 (74.3)	681 (64.5)		2,706	2,025 (67.8)	681 (64.5)	
TD, n (%)				0.33				0.74
Positive	143	112 (2.8)	31 (2.9)		111	80 (2.7)	31 (2.9)	
Negative	4,888	3,864 (97.2)	1,024 (97.1)		3,930	2,906 (97.3)	1,024 (97.1)	
CEA, n (%)				0.44				1.00
Positive	2,041	1,602 (40.3)	439 (41.6)		1,680	1,241 (41.6)	439 (41.6)	
Negative	2,990	2,374 (59.7)	616 (58.4)		2,361	1,745 (58.4)	616 (58.4)	
PNI, n (%)				0.33				0.66
Positive	387	314 (7.9)	73 (6.9)		266	193 (6.5)	73 (6.9)	
Negative	4,644	3,662 (92.1)	982 (93.1)		3,775	2,793 (93.5)	982 (93.1)	
Tumor size, n (%)				0.08				0.89
≤6 cm	4,080	3,204 (80.6)	876 (83.0)		3,348	2,472 (82.8)	876 (83.0)	
>6 cm	951	772 (19.4)	179 (17.0)		693	514 (17.2)	179 (17.0)	

PSM, propensity score matching; CRT, chemoradiotherapy; LNH, lymph node harvested; TD, tumor deposit; CEA, carcinoembryonic antigen; PNI, perineural invasion.

Table 2 Demographic and clinicopathologic data for surgery only group and neoadjuvant chemoradiotherapy + surgery + chemotherapy group before and after PSM

Variables	Before PSM				After PSM			
	No. of patients	Surgery only	Neoadjuvant CRT + surgery + CT	P value	No. of patients	Surgery only	Neoadjuvant CRT + surgery + CT	P value
No. of patients	4,523	3,976	547	–	2,150	1,603	547	–
Sex, n (%)				0.02				0.79
Male	2,784	2,423 (60.9)	361 (66.0)		1,407	1,046 (65.3)	361 (66.0)	
Female	1,739	1,553 (39.1)	186 (34.0)		743	557 (34.7)	186 (34.0)	
Age, n (%)				<0.01				0.80
<55 years	1,164	970 (24.4)	194 (35.5)		762	568 (35.4)	194 (35.5)	
55–64 years	1,251	1,065 (26.8)	186 (34.0)		710	524 (32.7)	186 (34.0)	
≥65 years	2,108	1,941 (48.8)	167 (30.5)		678	511 (31.9)	167 (30.5)	
Race, n (%)				0.90				0.94
White	3,637	3,197 (80.4)	440 (80.4)		1,736	1,296 (80.8)	440 (80.4)	
Black	366	324 (8.1)	42 (7.7)		158	116 (7.2)	42 (7.7)	
Other	520	455 (11.4)	65 (11.9)		256	191 (11.9)	65 (11.9)	
Grade, n (%)				0.34				0.89
I & II	4,115	3,611 (90.8)	504 (92.1)		1,976	1,472 (91.8)	504 (92.1)	
III & IV	408	365 (9.2)	43 (7.9)		174	131 (8.2)	43 (7.9)	
LNH, n (%)				<0.01				0.66
<12	1,218	1,022 (25.7)	196 (35.8)		752	556 (34.7)	196 (35.8)	
≥12	3,305	2,954 (74.3)	351 (64.2)		1,398	1,047 (65.3)	351 (64.2)	
TD, n (%)				0.18				0.81
Positive	133	112 (2.8)	21 (3.8)		77	56 (3.5)	21 (3.8)	
Negative	4,390	3,864 (97.2)	526 (96.2)		2,073	1,547 (96.5)	526 (96.2)	
CEA, n (%)				0.38				0.99
Positive	1,811	1,602 (40.3)	209 (38.2)		824	615 (38.4)	209 (38.2)	
Negative	2,712	2,374 (59.7)	338 (61.8)		1,326	988 (61.6)	338 (61.8)	
PNI, n (%)				0.40				0.80
Positive	363	314 (7.9)	49 (9.0)		185	136 (8.5)	49 (9.0)	
Negative	4,160	3,662 (92.1)	498 (91.0)		1,965	1,467 (91.5)	498 (91.0)	
Tumor size, n (%)				0.01				1.00
≤6 cm	3,669	3,204 (80.6)	465 (85.0)		323	1,362 (85.0)	465 (85.0)	
>6 cm	854	772 (19.4)	82 (15.0)		1,827	241 (15.0)	82 (15.0)	

PSM, propensity score matching; CRT, chemoradiotherapy; CT, chemotherapy; LNH, lymph node harvested; TD, tumor deposit; CEA, carcinoembryonic antigen; PNI, perineural invasion.

Table 3 Demographic and clinicopathologic data for surgery + chemotherapy group and neoadjuvant chemoradiotherapy + surgery + chemotherapy group before and after PSM

Variables	Before PSM				After PSM			
	No. of patients	Surgery + CT	Neoadjuvant CRT + surgery + CT	P value	No. of patients	Surgery + CT	Neoadjuvant CRT + surgery + CT	P value
No. of patients	823	276	547	–	589	237	352	–
Sex				<0.01				0.14
Male	512	151 (54.7)	361 (66.0)		358	135 (57.0)	223 (63.4)	
Female	311	125 (45.3)	186 (34.0)		231	102 (43.0)	129 (36.6)	
Age				0.461				0.74
<55 years	299	105 (38.0)	194 (35.5)		224	94 (39.7)	130 (36.9)	
55–64 years	268	82 (29.7)	186 (34.0)		181	69 (29.1)	112 (31.8)	
≥65 years	256	89 (32.2)	167 (30.5)		184	74 (31.2)	110 (31.2)	
Race				0.055				0.06
White	662	222 (80.4)	440 (80.4)		1736	188 (79.3)	281 (79.8)	
Black	74	32 (11.6)	42 (7.7)		158	30 (12.7)	28 (8.0)	
Other	87	22 (8.0)	65 (11.9)		256	19 (8.0)	43 (12.2)	
Grade				<0.01				0.69
I & II	735	231 (83.7)	504 (92.1)		534	213 (91.8)	321 (92.1)	
III & IV	88	45 (16.3)	43 (7.9)		55	24 (10.1)	31 (8.8)	
LNH				<0.01				0.23
<12	240	44 (15.9)	196 (35.8)		120	42 (17.7)	78 (22.2)	
≥12	583	232 (84.1)	351 (64.2)		469	195 (82.3)	274 (77.8)	
TD				0.52				0.98
Positive	35	14 (5.1)	21 (3.8)		21	9 (3.8)	12 (3.4)	
Negative	788	262 (94.9)	526 (96.2)		568	228 (96.2)	340 (96.6)	
CEA				0.09				0.99
Positive	297	88 (31.9)	209 (38.2)		186	75 (31.6)	111 (31.5)	
Negative	526	188 (68.1)	338 (61.8)		403	162 (68.4)	241 (68.5)	
PNI				0.80				0.37
Positive	76	27 (9.8)	49 (9.0)		51	17 (7.2)	34 (9.7)	
Negative	747	249 (90.2)	498 (91.0)		538	220 (92.8)	318 (90.3)	
Tumor size				0.01				0.67
≤6 cm	679	214 (77.5)	465 (85.0)		476	189 (79.7)	287 (81.5)	
>6 cm	144	62 (22.5)	82 (15.0)		113	48 (20.3)	65 (18.5)	

PSM, propensity score matching; CRT, chemoradiotherapy; CT, chemotherapy; LNH, lymph node harvested; TD, tumor deposit; CEA, carcinoembryonic antigen; PNI, perineural invasion.

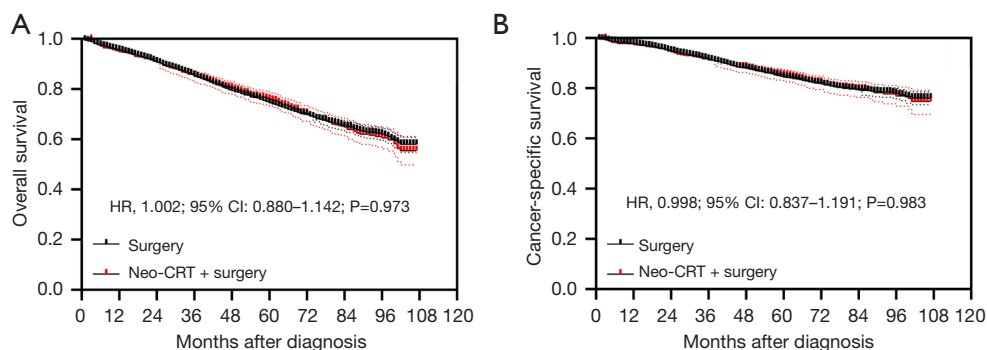


Figure 1 Survival curve: (A) overall survival of neoadjuvant chemoradiotherapy + surgery *vs.* surgery alone; (B) cancer-specific survival of neoadjuvant chemoradiotherapy + surgery *vs.* surgery alone. Neo-CRT, neoadjuvant chemoradiotherapy; HR, hazard ratio; CI, confidence interval.

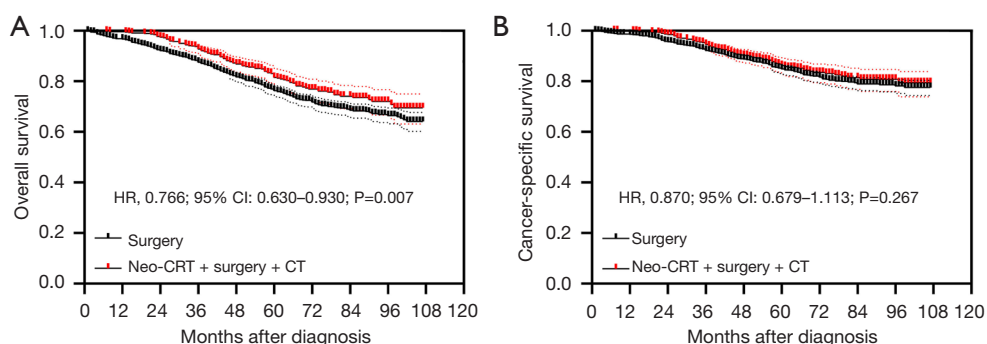


Figure 2 Survival curve: (A) overall survival of neoadjuvant chemoradiotherapy + surgery + chemotherapy *vs.* surgery alone; (B) cancer-specific survival of neoadjuvant chemoradiotherapy + surgery + chemotherapy *vs.* surgery alone. Neo-CRT, neoadjuvant chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; CI, confidence interval.

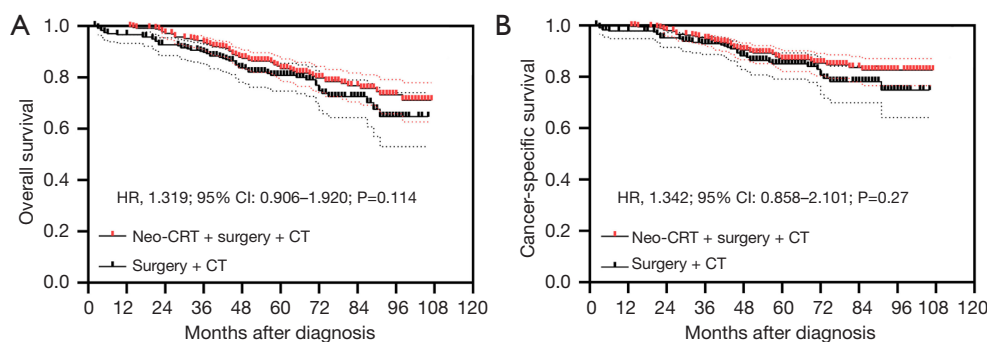


Figure 3 Survival curve: (A) overall survival of neoadjuvant chemoradiotherapy + surgery + chemotherapy *vs.* surgery + chemotherapy; (B) cancer-specific survival of neoadjuvant chemoradiotherapy + surgery + chemotherapy *vs.* surgery + chemotherapy. Neo-CRT, neoadjuvant chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; CI, confidence interval.

85.0% (95% CI: 79.1–89.3%) respectively.

Subgroup analysis of surgery alone vs. neoadjuvant CRT + surgery + chemotherapy

The univariate and multivariate Cox proportional risk regression were used to identify the preoperative independent risk factors for patients with stage IIA rectal cancer. And we performed a subgroup analysis for OS between the surgery group and the neoadjuvant CRT + surgery + chemotherapy group according to preoperative risk factors.

The univariate Cox proportional risk regression analysis showed that factors associated with OS included sex, age at diagnosis, race, histological grade, CEA level, LNH, TD, PNI, tumor size and perioperative therapy (Table 4). Of these, male sex, age >55 years, higher histological grade, less LNH, positive TD, positive CEA, positive PNI and tumor size >6 cm were risk factors associated with a decreased OS. Neoadjuvant CRT + surgery + chemotherapy was a protective factor associated with an increased OS compared with surgery alone. The results of the multivariate Cox proportional risk regression were similar to those of the univariate analysis (Table 4).

Based on multivariate Cox regression analysis, we defined age >55 years, grade III/IV, positive CEA and tumor size >6 cm as preoperative high-risk factors. Patients without these four high-risk factors were considered to be in the low-risk group and those containing at least one high-risk factor were considered to be in the high-risk group. After PSM, in the low-risk group, the Kaplan-Meier analysis showed that there was no statistically significant difference in OS between patients who underwent neoadjuvant CRT + surgery + chemotherapy and those who underwent surgery alone ($P=0.685$) (Figure 4A), and the 5-year OS was 85.8% (95% CI: 76.0–91.8%) and 89.4% (95% CI: 84.7–92.7%) respectively. In the high-risk group, the Kaplan-Meier analysis showed that patients treated with neoadjuvant CRT + surgery + chemotherapy had better OS than those treated with surgery alone ($P=0.003$) (Figure 4B). Moreover, patients treated with neoadjuvant CRT + surgery + chemotherapy had better OS than those treated with surgery alone in either the subgroup containing one high-risk factor ($P=0.046$) (Figure 4C) or the subgroup containing more than one high-risk factor ($P=0.025$) (Figure 4D).

Discussion

In the last two decades, multimodal treatment including neoadjuvant CRT has been widely used for LARCs (11). However, this treatment strategy has an important disadvantage, namely the high risk of intraoperative or postoperative complications. The adverse reactions of neoadjuvant CRT may lead to a financial burden and a decline in quality of life, and delay follow-up treatment (12). Therefore, for some LARCs in earlier stages, such as stage IIA, whether neoadjuvant therapies should be completed is controversial in different studies and literature. Some studies have suggested that patients with T3N0 and T1–3N1–2 rectal cancer judged by imaging should receive neoadjuvant CRT (7). Benson *et al.* pointed out that in patients with cT3/T4 or lymph node-positive rectal cancer, preoperative therapy reduces local recurrence and improves tumor prognosis according to the NCCN guidelines (13). There is growing evidence that patients with LARC benefit more from neoadjuvant CRT than surgery alone or postoperative CRT in terms of local control rates and sphincter protection (14). However, some studies have indicated that T3N0 rectal cancer patients can control local recurrence at a relatively low level with surgery alone, suggesting that these patients may not need neoadjuvant CRT (15). Although neoadjuvant CRT significantly reduced the risk of local recurrence in LARCs, the benefit of local control did not translate into a survival benefit (9). Therefore, it remains controversial whether neoadjuvant CRT provides sufficient benefit to outweigh the side effects and inconvenience of treatment for patients with stage IIA rectal cancer (15).

Our results showed that there was no significant difference in either OS or CSS between patients who underwent neoadjuvant CRT + surgery and those who underwent surgery alone. However, patients with stage IIA rectal cancer treated with neoadjuvant CRT + surgery + chemotherapy had better OS than those treated with surgery alone. But the CSS of the neoadjuvant CRT + surgery + chemotherapy group did not show superiority than that of the surgery alone group. Therefore, our study concluded that for patients with stage IIA rectal cancer, neoadjuvant CRT + surgery is not effective in improving the long-term survival of patients. But neoadjuvant CRT + surgery + chemotherapy can improve the OS of stage IIA patients.

Table 4 Univariate and multivariate analysis of OS in patients with stage IIA rectal cancer (Cox risk regression model)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.000	Reference		1.000	Reference	
Male	1.241	1.109–1.388	<0.001	1.247	1.127–1.380	<0.001
Age						
<55 years	1.000	Reference		1.000	Reference	
55–64 years	1.429	1.180–1.731	<0.001	1.381	1.166–1.635	<0.001
≥65 years	2.723	2.402–3.086	<0.001	3.286	2.842–3.800	<0.001
Race						
White	1.000	Reference		1.000	Reference	
Black	1.152	0.966–1.375	0.115	1.220	1.032–1.441	0.02
Other	0.810	0.695–0.945	0.007	0.823	0.696–0.973	0.023
Grade						
I & II	1.000	Reference		1.000	Reference	
III & IV	1.551	1.278–1.882	<0.001	1.359	1.174–1.572	<0.001
CEA						
Negative	1.000	Reference		1.000	Reference	
Positive	1.560	1.394–1.746	<0.001	1.464	1.329–1.613	<0.001
PNI						
Negative	1.000	Reference		1.000	Reference	
Positive	1.782	1.443–2.202	<0.001	1.449	1.238–1.696	<0.001
TD						
Negative	1.000	Reference		1.000	Reference	
Positive	2.660	1.894–3.735	<0.001	1.984	1.601–2.458	<0.001
LNH						
≤12	1.000	Reference		1.000	Reference	
>12	0.783	0.693–0.885	<0.001	0.805	0.726–0.892	<0.001
Size						
≤6 cm	1.000	Reference		1.000	Reference	
>6 cm	1.283	1.112–1.480	<0.001	1.310	1.163–1.474	<0.001
Perioperative therapy						
Neoadjuvant CRT + surgery	1.000	Reference		1.000	Reference	
Surgery alone	1.038	0.917–1.175	0.664	1.041	0.918–1.180	0.533
Neoadjuvant CRT + surgery + CT	0.672	0.550–0.821	0.001	0.726	0.584–0.903	0.004
Surgery + CT	0.766	0.595–0.986	0.039	0.836	0.632–1.105	0.208

OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; CEA, carcinoembryonic antigen; PNI, perineural invasion; TD, tumor deposit; LNH, lymph node harvested; CRT, chemoradiotherapy; CT, chemotherapy.

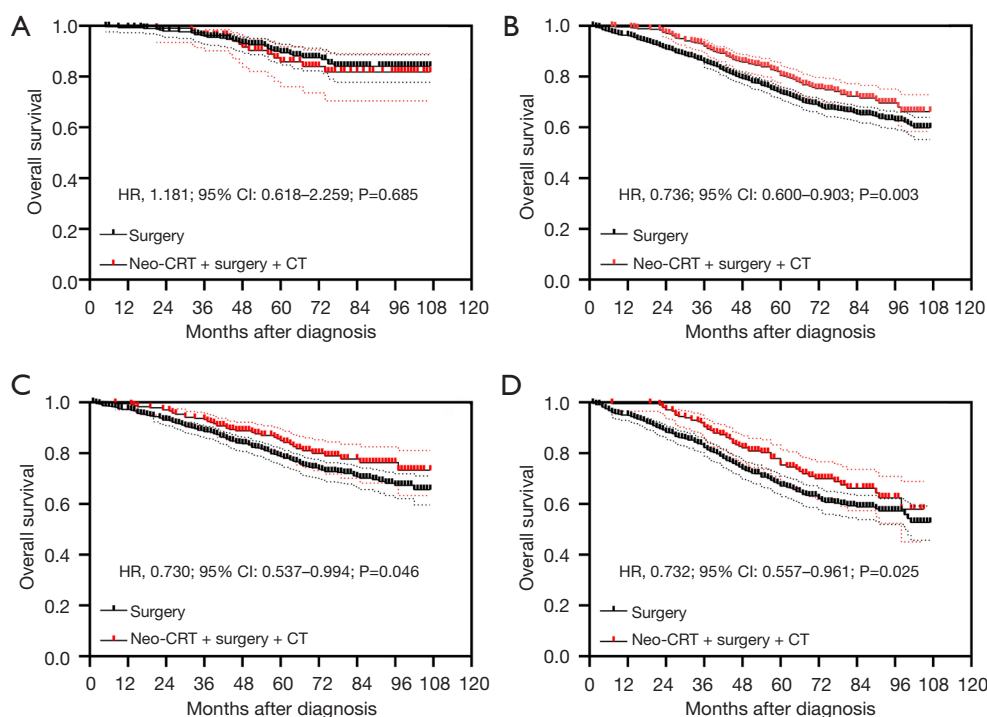


Figure 4 Overall survival curve of neoadjuvant chemoradiotherapy + surgery + chemotherapy vs. surgery alone: (A) low-risk subgroup; (B) high-risk subgroup; (C) high-risk subgroup with one preoperative risk factor; (D) high-risk subgroup with more than one preoperative risk factor. Neo-CRT, neoadjuvant chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; CI, confidence interval.

However, do all patients with stage IIA rectal cancer need neoadjuvant and adjuvant treatment? What patients could be exempt from perioperative therapy? As we know, the severe toxicity associated with neoadjuvant CRT, including complications such as structural fractures of the lumbar spine, sexual and urinary dysfunction, proctitis, significant increases in defecation times, and incontinence (16), presents a significant obstacle and distress to the patient's subsequent recovery and quality of survival.

The ESMO guidelines for the treatment of rectal cancer recommend a neoadjuvant treatment strategy based on multiple factors such as tumor location, circumferential resection margin (CRM), and clinical stage (17). This is specifically indicated for patients with low-risk rectal cancer who meet the following criteria: early T3N0, tumor invasion <5 mm, no significant invasion of the mesorectal fascia (MRF), no neurovascular invasion, and other factors; direct surgical treatment can be considered, and adjuvant treatment such as chemotherapy could be considered if postoperative pathology suggests including high-risk factors (8). Lin *et al.* also stated that the risk of colorectal cancer depends on the lymph node metastasis,

positive CRM and distal resection margin (18). Skancke *et al.* noted that the short distal margin, lymph node metastasis, and positive CRM were significant predictors of local recurrence, distant metastasis, and OS (19). The prognosis of T3 patients with infiltration of more than 5 mm is significantly worse than that of patients with infiltration of less than 5 mm, and neoadjuvant CRT is usually required (7). Studies have shown that CRM is an important independent prognostic factor for local recurrence and long-term survival (20,21). Neoadjuvant radiotherapy should be considered if the distance between the tumor and rectal mesenteric fascia is predicted to be <1 mm on preoperative magnetic resonance imaging (MRI) (22). Studies have shown that in early, favorable cases (e.g., some early cT3N0), TME surgery alone is appropriate (15). For middle and lower stage II and III rectal cancer, preoperative radiotherapy or CRT can reduce the local recurrence rate without improving OS (23). Lavryk *et al.* showed that the distance between the tumor and anal verge was an independent prognostic parameter (24). Therefore, these factors could be considered when assessing the need for neoadjuvant therapy in stage IIA patients.

Unconditional application of neoadjuvant CRT in low-risk patients was likely to result in overtreatment (18). Our study also performed a subgroup analysis to explore the effects of neoadjuvant and adjuvant therapy in different risk groups. The results showed that neoadjuvant CRT + surgery + chemotherapy did not significantly improve OS in the low-risk subgroup, but significantly improved OS in the high-risk subgroup regardless of the number of preoperative risk factors. Because we need to judge whether to use neoadjuvant treatment preoperatively, we chose risk factors among the preoperative independent factors, rather than postoperative ones.

For adjuvant treatment, we only included the most commonly used adjuvant chemotherapy. Baek *et al.* stated that in patients with low-lying rectal cancer, adjuvant CRT reduced local recurrence rates (25). In contrast, de Paula *et al.* showed that adjuvant CT did not prolong OS compared with adjuvant chemotherapy for T3N0 patients (26). We compared the patients who received neoadjuvant CRT + surgery + chemotherapy and those who received surgery + chemotherapy, the results showed that although there was no statistical difference in OS and CSS between the two groups, the OS of the neoadjuvant CRT + surgery + chemotherapy group was significantly higher than that of the surgery + chemotherapy group. In addition, multivariate analysis showed that OS in the neoadjuvant CRT + surgery + chemotherapy group was statistically superior to that in the neoadjuvant CRT + surgery group and the surgery alone group, while the surgery + chemotherapy group was not. Therefore, we think that the long-term survival of the surgery + chemotherapy group may be better than that of the neoadjuvant CRT + surgery group and the surgery alone group, but the long-term survival of the neoadjuvant CRT + surgery + chemotherapy group is much better.

The strength of this study is the large sample size available from the SEER database, which contains a wide range of information on neoadjuvant and adjuvant therapy for analysis and comparison, and increases the persuasiveness of this study. However, this study has some limitations. First, the SEER database only covers 27.8% of the US population, and many patients migrated in and out of SEER registry areas. So, there may be some bias in the inclusion and selection of data. Second, some key data that may affect the outcome of prognosis cannot be obtained from the SEER database, like underreported and incomplete data regarding adjuvant therapy and unrecorded variables, for example, (I) CRM. Although we did not have access to CRM data, its role as an independent postoperative risk

factor did not provide guidance on whether to perform neoadjuvant therapy. (II) Depth of tumor invasion into the MRF. MRF, which obtained by pelvic MRI, may provide some guidance on neoadjuvant treatment for rectal cancer. (III) Where the tumor is located. Third, SEER database only includes the final pathologic stage, which may include patients who had a higher clinical stage, received neoadjuvant treatment, and then were downstaged at the time of resection. However, patients with higher stage usually have a poorer prognosis. If the results containing these patients were still significantly different, this would indicate the robustness of the results. Forth, patients with insufficient information were excluded, and it is unclear whether the results apply to them. Finally, this was a retrospective cohort study with a lower level of evidence than the randomized controlled trials. However, the application of PSM to reduce the influence of confounding factors can also increase the persuasiveness of the study.

Conclusions

In conclusion, there is no evidence that neoadjuvant CRT + surgery can significantly improve OS and CSS compared to surgery alone in patients with stage IIA rectal cancer. Compared to surgery alone, neoadjuvant CRT + surgery + chemotherapy can improve OS, but only in patients with preoperative risk factors. So, we suggest that patients with no preoperative high-risk factor may be considered for surgery alone, patients with preoperative risk factors need to be considered for neoadjuvant CRT + surgery + chemotherapy to improve OS.

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Footnote

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have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since the data of this project were all extracted from the SEER database and did not involve patient safety, privacy, and postoperative follow-up, no informed consent and no ethics committee approval were required.

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