Original Article

Endoscopic resection *vs.* endoscopic resection plus chemoradiation for T1 stage colorectal cancer: a real-world retrospective cohort study

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Background: Early-stage colorectal cancer (CRC) patients treated with either endoscopic resection (ER) alone or combined ER with chemoradiotherapy (CRT) have unknown survival rates. A national descriptive epidemiological study was conducted to compare the long-term survival of patients with T1 stage CRC with or without the two different treatment options.

Methods: Our study identified the records of patients with T1-stage CRC between 2010 and 2018 by searching the Surveillance, Epidemiology, and End Results (SEER) database. Long-term survival was compared using Kaplan-Meier methods and Cox proportional hazard models based on patient demographic and cancer parameters.

Results: After propensity score matching (PSM), 825 T1-stage CRC patients were finally enrolled in this study, with 718 patients treated with ER and 107 patients treated with ER + CRT. The overall survival (OS) and cancer specific survival (CSS) rates were similar between the two treatment options (OS: P=0.47; CSS: P=0.28). According to subgroup analysis, older patients and patients with rectal tumor locations exhibited significantly higher OS and CSS rates in the ER + CRT group than in the ER group (OS: P<0.0001; CSS: P<0.0001).

Conclusions: The findings from the SEER database showed that OS and CSS rates were similar between the ER and ER + CRT treated groups. Older patients and patients with rectal cancer benefited the most from ER + CRT treatment.

Keywords: Colorectal cancer (CRC); T1 stage; endoscopic resection (ER); chemoradiotherapy (CRT); Surveillance, Epidemiology, and End Results (SEER)

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Introduction

There are approximately 1–2 million new cases of colorectal cancer (CRC) every year, and approximately 600,000 people die of this disease. CRC ranks third among the most common cancers and fourth in the list of most common causes of cancer death worldwide (1). Through early screening, the detection rate of early CRC has recently increased (2). Patients with CRC in the early stage have a significantly better prognosis than those in the advanced stage (3). Early CRC, as such, includes carcinomas confined to the mucosa (Tis, tumors confined to the mucosa, not inserted into the lamina muscularis

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mucosae) and submucosa (T1, infiltration through lamina muscularis mucosae into submucosa, no infiltration of lamina muscularis propria), regardless of lymph node involvement (4).

At present, endoscopic resection (ER) is one of the best options for the large adenomas and selected early CRC excision (5). Regarding the complication rate, quality of life, hospital stay, morbidity rate, and mortality rate, ER has more advantages in early CRC treatment compared to surgical resection (6). However, due to the high local recurrence rate and the risk of lymph node metastasis of ER for early CRC, there is still controversy regarding the application of ER in the treatment of early CRC (7,8). Some research suggested that inadequate endoscopic treatment for T1 stage CRC would accelerate the malignant potential of CRC and increase the risk of metastasis (8,9). The latest international guidelines recommend ER for T1 CRC with histological features of low risk and additional surgical resection for those at high risk of lymph node metastases (10). However, in actual clinical practice, many patients may be unfit for or decline radical surgery. In recent years, adjuvant chemoradiotherapy (CRT) after ER has been considered as an alternative to radical surgery for these patients (11).

However, no studies have specifically addressed the survival rate of CRC patients treated with ER alone or combined CRT and ER, especially in early stage. Therefore, we performed a national descriptive epidemiological study by using the Surveillance, Epidemiology, and End Results (SEER) database to compare the effect of different treatment options on long-term survival in patients with T1 stage CRC by conventional and propensity score matching (PSM) approaches. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1411/rc).

Highlight box

Key findings

- We found that the overall survival (OS) and cancer specific survival (CSS) rates were similar between endoscopic resection (ER) group and ER+ chemoradiotherapy (CRT) group.
- Older patients and patients with rectal cancer benefited the most from ER + CRT treatment.

What is known and what is new?

- Endoscopic resection has become one of the most important treatments in early-stage colorectal cancer.
- ER and ER + CRT have similar OS and CSS rates, however, older patients and rectal cancer patients were benefit from ER + CRT treatment.

What is the implication, and what should change now?

- Most younger patients and colon cancer patients can be free from CRT after ER, while older patients and rectal cancer patients should be carefully evaluated.

Methods

Study population and data source

We conducted a real-world retrospective cohort study using "SEER Research Plus Data, 18 registries, November 2020 sub (2000–2018) Database" (https://seer.cancer.gov/). The inclusion criteria were as follows: (I) patients with adenocarcinoma of TisM0 or T1M0 CRC (no invasion beyond the submucosa); (II) patients treated with ER or ER plus radiotherapy, chemotherapy or CRT. Exclusion criteria included the following: (I) age less than 18 years; (II) histological types other than adenocarcinoma; (III) metastatic cancer; (IV) patients with missing or unknown information; and (V) tumor diagnosed solely on autopsy or death certificate. Tumor node metastasis (TNM) stage was determined by the 7th edition American Joint Committee on Cancer (AJCC).

Data regarding characteristics of the patient at baseline (age, sex, race, year of diagnosis), clinical and histological parameters (tumor size, lymph node metastasis, grade, TNM stage, treatment options), cancer specific survival (CSS) or overall survival (OS), survival months and status were recorded. T1 stage CRC patients ('C18.0-C20.0 colon and rectum' of ICD-O-3) were selected for further analysis. The patients were dichotomized according to the treatment options: ER alone and ER combined with CRT. The flow diagram of patient selection is shown in *Figure 1*.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We collected data from population-based cancer registries with anonymous information. The SEER database contains data for public use, so there was no need for approval or declaration of local ethics for our study.

Statistical analysis

Data were extracted by using the SEER*Stat program version 8.3.9. Statistical analysis was performed by using Statistics, Version 26.0 (SPSS, Chicago, IL, USA) and R software (version 3.5.1, http://www.R-project.org/).

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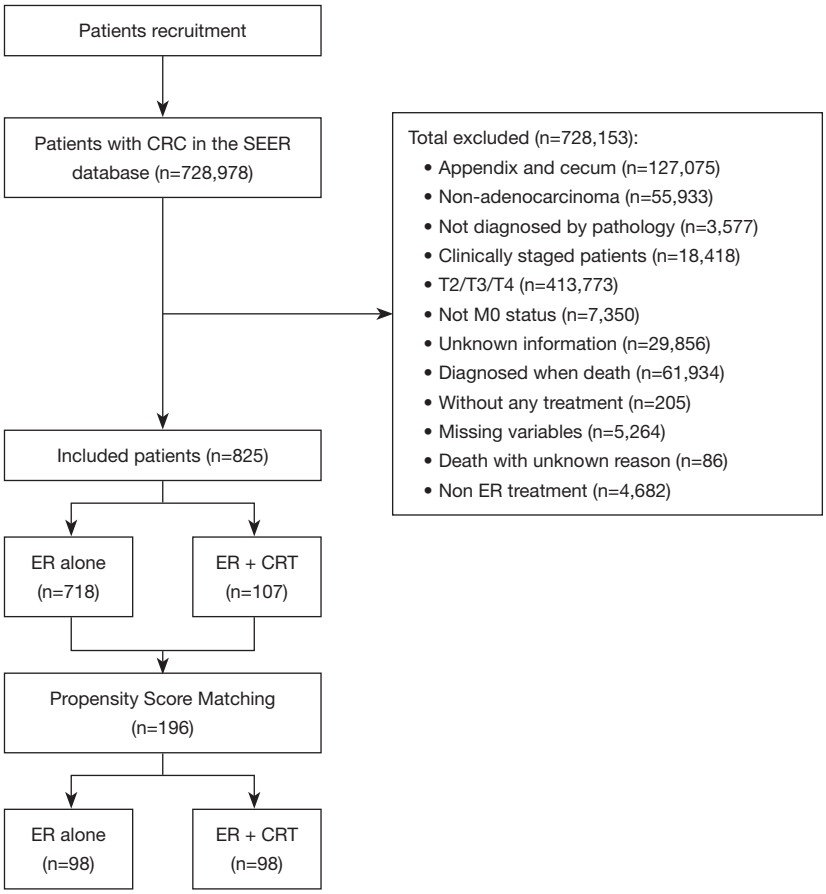

Figure 1 The flowchart of study population selection. CRC, colorectal cancer; SEER, Surveillance, Epidemiology, and End Results; ER, endoscopic resection; CRT, chemoradiotherapy.

PSM was conducted to calibrate the effects of the baseline clinicopathological differences. The match ratio of patients in both the surgery and ET groups was 1:1, with 0.01 of match tolerance. The R*C Chi-squared test was applied for comparison of categorical characteristics. The Kaplan-Meier method and the log-rank test were applied for survival analysis. In addition to the 3- and 5-year OS and CSS, the multivariate Cox proportional hazard test was used by including variables with P values of 0.1. Tests were two-sided with a significance level of $P<0.05$. Subgroup Cox regression analysis was further performed for the following subgroups: age, tumor location, tumor size, stage and invasion depth.

Results

Baseline characteristics of the ER and ER + CRT groups

A total of 825 patients (ER group: n=718, 87.0%; ER + CRT group: n=107, 13.0%) were recruited from the SEER database. Patients 60 years old or older accounted for 73.21% (604/825). The majority of patients were non-Asian Pacific Islanders (APIs) (93.70%, 773/825). A total of 760 patients exhibited grade I–II histology, and 65 patients exhibited grade III–IV histology. Considering nodal status, most patients were N0. Regarding tumor location, tumors were in the colon in 319 patients, and they were in the rectum in 506 patients. In terms of tumor stage, most patients were in stage 1 (699/825, 84.73%). The detailed baseline characteristics and tumor indices are shown in *Table 1*. Significant differences regarding marital status, tumor size, histological grade, node status, tumor location, tumor stage and T stage ($P<0.05$) were found. Consequently, PSM analysis was performed to generate balanced cohorts in the ER group *vs.* the ER + CRT group to minimize confounding bias.

The ratio of patients who underwent ER + CRT from

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Table 1 Baseline characteristics of the two groups

Variables	ER (n=718)	ER + CRT (n=107)	P
Age (years)			0.058
20–59	188 (85.1)	33 (14.9)	
60–79	388 (86.0)	63 (14.0)	
≥80	142 (92.8)	11 (7.2)	
Marital status			0.027
Unmarried	274 (90.4)	29 (9.6)	
Married	444 (85.1)	78 (14.9)	
Sex			0.089
Male	373 (85.2)	65 (14.8)	
Female	345 (89.1)	42 (10.9)	
Race			0.336
Non-API	675 (87.3)	98 (12.7)	
API	43 (82.7)	9 (17.3)	
Tumor size (cm)			<0.001
<2	557 (90.3)	60 (9.7)	
2–5	149 (78.4)	41 (21.6)	
>5	12 (66.7)	6 (33.3)	
Histological grade			<0.001
Grade I–II	671 (88.3)	89 (11.7)	
Grade III–IV	47 (72.3)	18 (27.7)	
Nodal status			0.003
N0	716 (87.4)	103 (12.6)	
N1–3	2 (33.3)	4 (66.7)	
Location			<0.001
Colon	311 (97.5)	8 (2.5)	
Rectum	407 (80.4)	99 (19.6)	
Stage			<0.001
0	100 (95.2)	5 (4.8)	
1	602 (86.1)	97 (13.9)	
2	14 (93.3)	1 (6.7)	
3	2 (33.3)	4 (66.7)	
T stage			0.007
Tis	100 (95.2)	5 (4.8)	
T1	618 (85.8)	102 (14.2)	

Categorical data were presented as n (%). ER, endoscopic resection; CRT, chemoradiotherapy; API, Asian Pacific Islander.

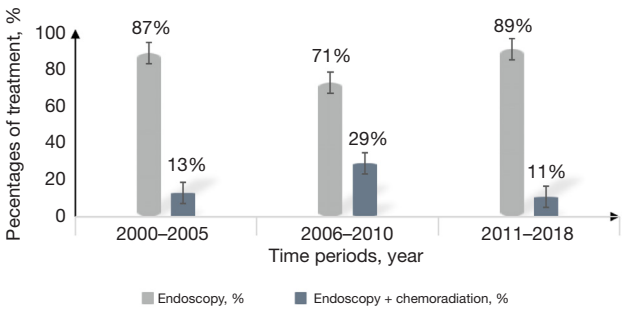

Figure 2 Changes in use of ER and ER + CRT in 2000–2005, 2006–2010 and 2011–2018. ER, endoscopic resection; CRT, chemoradiotherapy.

the year of diagnosis in 2006–2010 was slightly but not significantly higher than that in 2000–2005 (P=0.097) and 2011–2018 (P=0.192). The overall rate of patients who underwent ER + CRT and ER in the 18 years was similar (P>0.05) (*Figure 2*).

ER group vs. ER + CRT group after PSM

After two balanced cohorts were generated and PSM analysis was performed, we found no significant difference in age (P=0.190), sex (P=0.662), race (P=0.621), tumor size (P=0.122), stage (P=0.118), location (P=0.435), marital status (P=0.215) or T stage (P=0.212) (*Table 2*). The OS and CSS rates of the two groups before PSM (*Figure 3A,3B*) and after PSM (*Figure 3C,3D*) are shown. We found that the OS and CSS rates of the two treatment options after PSM were similar (OS: P=0.47; CSS: P=0.28). As there was a small number of colon cancer patients after PSM, we also evaluated the OS and CSS of rectal cancer patients in the two groups separately, and similar results are shown in Figure S1.

In univariate analysis, we found that age and tumor location were significant prognostic factors of CSS. In multivariate Cox regression, age, tumor stage and tumor location were significant prognostic factors of CSS (*Table 3*, *Figure 4A*). In univariate analysis, we found that age, marital status and tumor location were significant prognostic factors of OS. In multivariate Cox regression, older age, invasion depth, tumor stage and tumor location were significant prognostic factors of OS (*Table 3*, *Figure 4B*).

Subgroup analysis

Subgroup analysis suggested that in patients with tumors

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Table 2 Characteristics of patients treated with ER and ER + CRT for T1 stage CRC after PSM

Variables	Matched cohort		
	ER, n=98	ER + CRT, n=98	P
Age at diagnosis (years)			0.190
20–59	37 (54.4)	31 (45.6)	
60–79	45 (44.1)	57 (55.9)	
≥80	16 (61.5)	10 (38.5)	
Sex			0.662
Female	38 (48.1)	41 (51.9)	
Male	60 (51.3)	57 (48.7)	
Race			0.621
Non-API	88 (49.4)	90 (50.6)	
API	10 (55.6)	8 (44.4)	
Tumor size (cm)			0.122
<2	50 (47.2)	56 (52.8)	
2–5	48 (55.2)	39 (44.8)	
>5	0	3 (100.0)	
Histological grade			0.04
Grade I–II	92 (52.9)	82 (47.1)	
Grade IV	6 (27.3)	16 (72.7)	
Stage			0.118
0	1 (16.7)	5 (83.3)	
1–2	97 (51.3)	92 (48.7)	
3	0	1 (100.0)	
Location			0.435
Colon	10 (62.5)	6 (37.5)	
Rectum	88 (48.9)	92 (51.1)	
Nodal status			
N0	98 (100.0)	98 (100.0)	NA
N1–3	NA	NA	
T stage			0.212
Tis	1 (16.7)	5 (83.3)	
T1	97 (51.1)	93 (48.9)	
Marital status			0.215
Unmarried	34 (56.7)	26 (43.3)	
Married	64 (47.1)	72 (52.9)	

Categorical data were presented as n (%). ER, endoscopic resection; CRT, chemoradiation; CRC, colorectal cancer; PSM, propensity score matching; API, Asian Pacific Islander; NA, not applicable.

located in the rectum, the OS and CSS rates in the ER + CRT group were significantly higher than those in the ER group (OS: P=0.0074, CSS: P=0.0041) (*Figure 5A-5D*). Subgroup analysis suggested that in older patients, the OS and CSS rates in the ER + CRT group were also significantly higher than those in the ER group (OS: P<0.0001; CSS: P<0.0001) (*Figure 5E-5H*).

Other subgroup analyses, such as tumor size (OS: P=0.64; CSS: P=0.63) (Figure S2), stage (OS: P=0.32; CSS: P=0.1) (Figure S3) and invasion depth (OS: P=0.33; CSS: P=0.11) (Figure S4), showed no significant difference between the two groups in terms of OS and CSS.

Discussion

In recent years, ER has become the first choice of treatment option in early-stage CRC. Two large-scale multi-center studies in Japan conducted long-term follow-up of patients with submucosal invasive CRC undergoing ER (12,13). The long-term prognosis of patients with negative vertical margins, medium or highly differentiated adenocarcinoma, no lymphatic vessel invasion and submucosal invasion depth less than 100 μm (low-risk group) after ER was equivalent to that of patients without additional surgery. However, there are many factors relating to a high local recurrence rate after ER for early CRC, of which potential lymph node metastasis accounts for the top reason (14). In some cases, metastatic lymph nodes are similar to normal lymph nodes in size and are very difficult to diagnose and cannot be identified by preoperative imaging examinations. The inaccurate preoperative tumor staging may be due to limited clinical imaging (15). Consequently, histopathological examinations of CRC specimens after ER are found to be more advanced than preoperative predictions. Sometimes, it has unforeseen adverse features, such as submucosal invasion >1 mm, poor differentiation or undifferentiation, lymphovascular invasion (LVI), perineural invasion, all of which are related to tumor relapse (16). According to the National Comprehensive Cancer Network (NCCN) guidelines, patients with stage T1 CRC and the aforementioned high-risk characteristics should undergo additional surgery after ER. There are, however, several reasons why patients in clinical practice may not be medically suitable for radical surgery or refuse it, such as a strong willingness to preserve the anus, a high mortality rate and surgery-related complications (17).

In our study, we found that the OS rate and CSS rate were similar between ER group and ER + CRT group,

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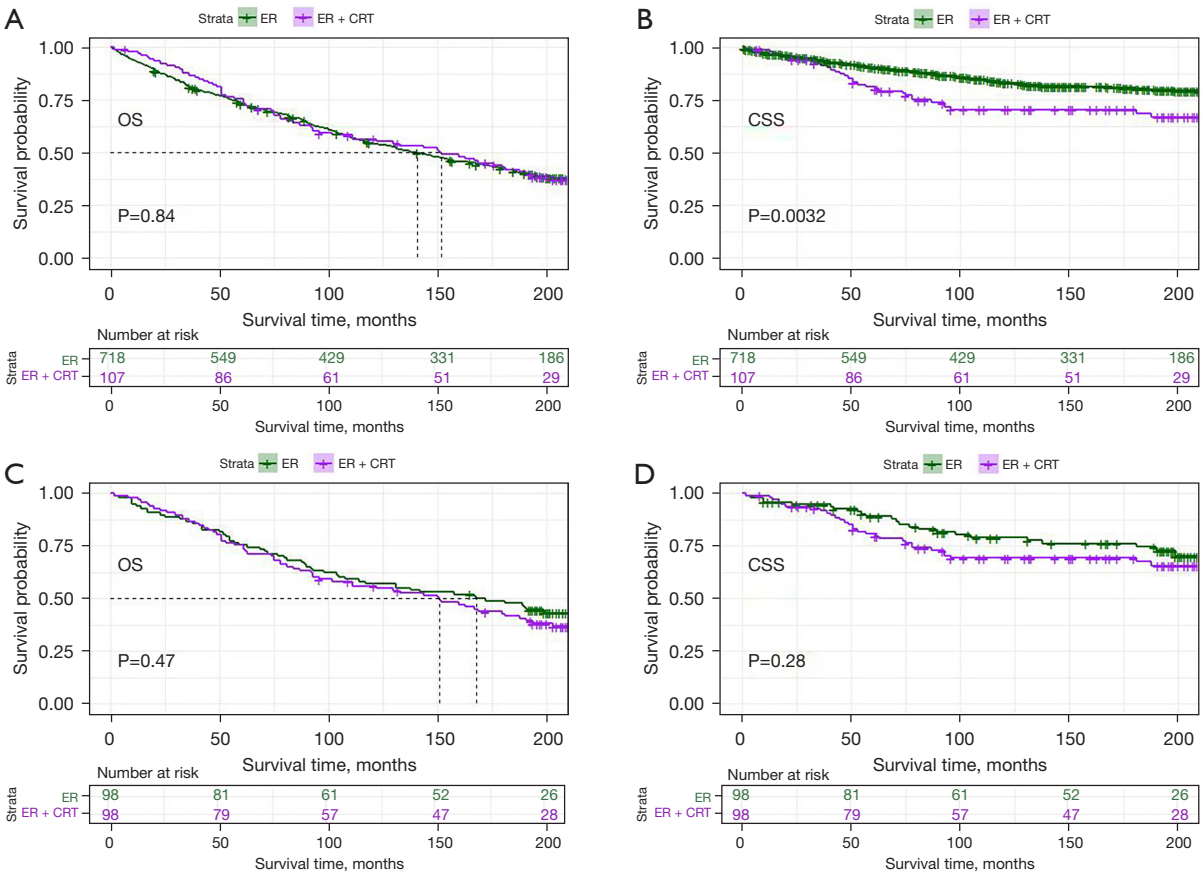

Figure 3 The OS and CSS rates of the two groups. (A) The OS rate before PSM; (B) The CSS rate before PSM; (C) the OS rate after PSM; (D) the CSS rate after PSM. ER, endoscopic resection; CRT, chemoradiotherapy; OS, overall survival; CSS, cancer specific survival; PSM, propensity score matching.

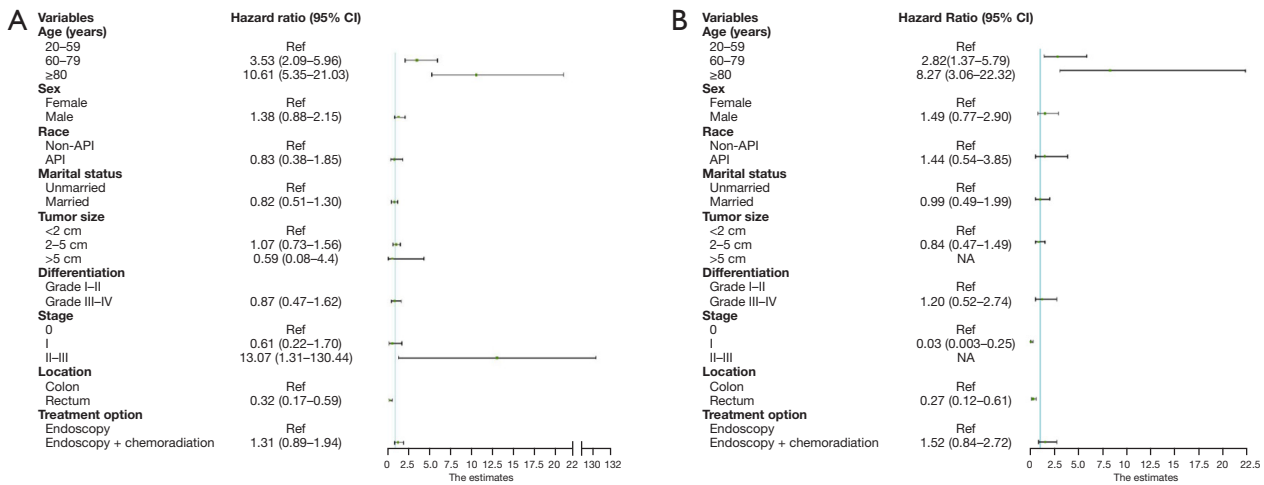

Figure 4 The forest plot of multiple cox regression of two groups. (A) Age, tumor stage and tumor location were significant prognostic factors of CSS in multivariate Cox regression. (B) Older age, invasion depth, tumor stage and tumor location were significant prognostic factors of OS. CI, confidence interval; OS, overall survival; CSS, cancer specific survival; API, Asian Pacific Islander.

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Table 3 Univariate and multivariate analyses of OS and CSS in patients with T1 stage CRC treated with ER and ER + CRT after PSM

Variables	Univariate analysis				Multivariate analysis			
	CSS		OS		CSS		OS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)								
20–59	Ref		Ref		Ref		Ref	
60–79	2.211 (1.133–4.317)	0.020	3.181 (1.931–5.237)	<0.001	2.821 (1.373–5.795)	0.005	3.531 (2.092–5.959)	<0.001
≥80	4.768 (2.027–11.215)	<0.001	8.642 (4.729–15.792)	<0.001	8.266 (3.061–22.324)	<0.001	10.606 (5.350–21.025)	<0.001
Sex								
Female	Ref		Ref		Ref		Ref	
Male	1.113 (0.639–1.940)	0.706	0.971 (0.670–1.409)	0.879	1.497 (0.772–2.901)	0.232	1.375 (0.880–2.147)	0.162
Race								
Non-API	Ref		Ref		Ref		Ref	
API	0.830 (0.330–2.089)	0.693	0.492 (0.229–1.058)	0.069	1.444 (0.541–3.853)	0.463	0.833 (0.376–1.847)	0.653
Marital status								
Unmarried	Ref		Ref		Ref		Ref	
Married	0.842 (0.473–1.501)	0.560	0.639 (0.438–0.934)	0.021	0.989 (0.490–1.998)	0.976	0.817 (0.511–1.304)	0.396
Tumor size (cm)								
<2	Ref		Ref		Ref		Ref	
2–5	0.957 (0.554–1.654)	0.876	1.147 (0.794–1.659)	0.465	0.839 (0.473–1.487)	0.547	1.065 (0.729–1.556)	0.744
>5	NA	NA	0.544 (0.075–3.925)	0.546	NA	NA	0.594 (0.080–4.396)	0.610
Histological grade								
Grade I–II	Ref		Ref		Ref		Ref	
Grade III–IV	1.253 (0.566–2.776)	0.578	0.974 (0.535–1.771)	0.930	1.198 (0.524–2.737)	0.669	0.873 (0.469–1.623)	0.667
Nodal status								
N0	Ref	–	Ref	–	Ref	–	Ref	–
T stage								
Tis	Ref	–	Ref	–	Ref	–	Ref	–
T1a	0.402 (0.125–1.289)	0.125	0.610 (0.225–1.655)	0.331	16.198 (1.371–191.416)	0.027	NA	NA
Stage								
0	Ref		Ref		Ref		Ref	
1–2	0.394 (0.123–1.265)	0.118	0.604 (0.223–1.641)	0.323	0.027 (0.003–0.253)	0.002	0.606 (0.216–1.697)	0.340
3	3.816 (0.387–37.670)	0.252	3.212 (0.353–29.204)	0.300	NA	NA	13.073 (1.310–130.438)	0.029
Location								
Colon	Ref		Ref		Ref		Ref	
Rectum	0.348 (0.164–0.740)	0.006	0.463 (0.259–0.826)	0.009	0.266 (0.117–0.606)	0.002	0.318 (0.171–0.590)	<0.001
Treatment option								
ER	Ref		Ref		Ref		Ref	
ER + CRT	1.346 (0.782–2.318)	0.283	1.143 (0.793–1.639	0.473	1.515 (0.844–2.721)	0.164	1.313 (0.888–1.942)	0.173

OS, overall survival; CSS, cancer-specific survival; CRC, colorectal cancer; ER, endoscopic resection; CRT, chemoradiation; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; API, Asian Pacific Islander; NA, not applicable.

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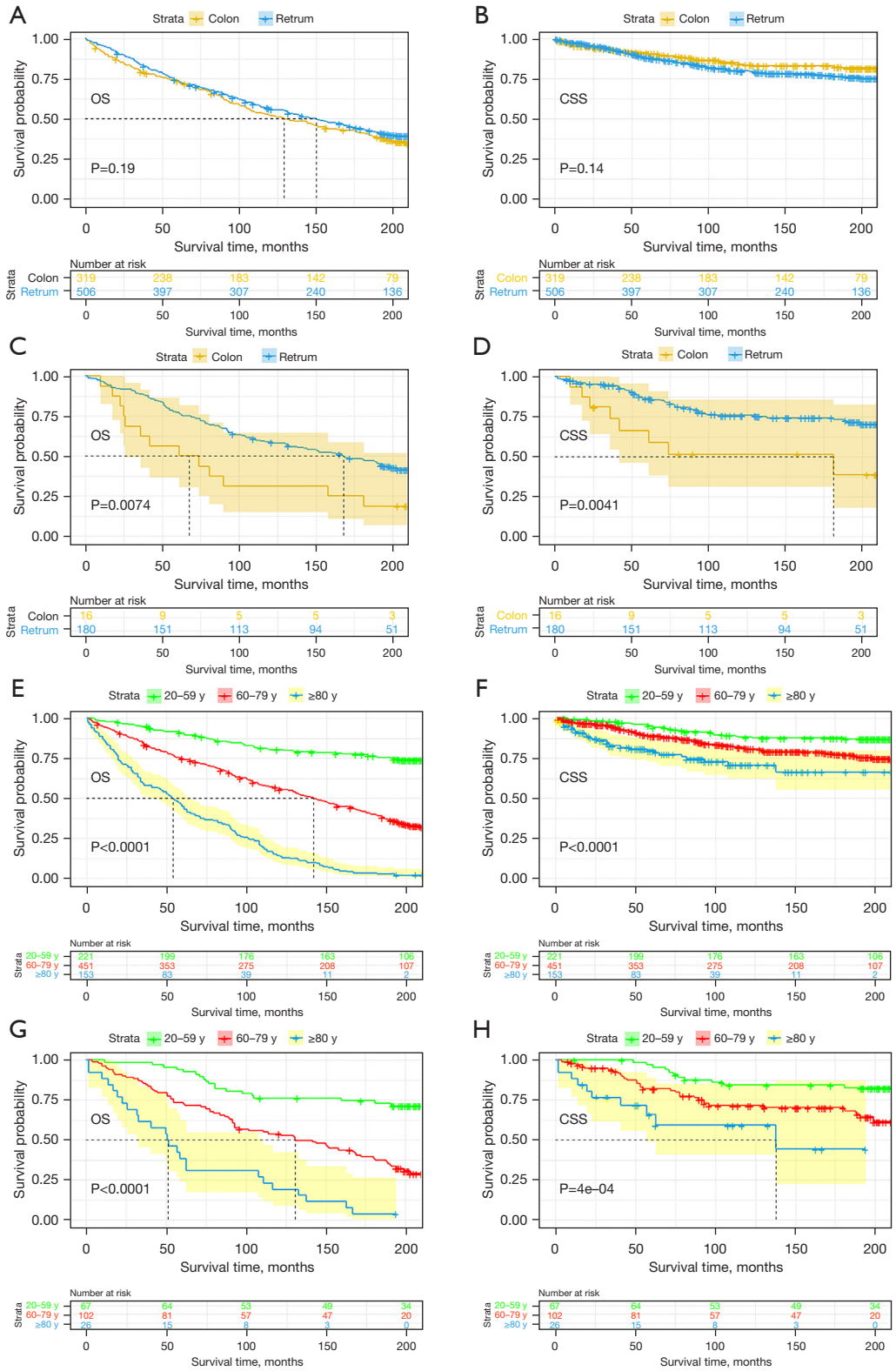

Figure 5 The OS and CSS rates in ER + CRT *vs.* ER group in subgroup analysis. (A-D) Subgroup analysis in patients with tumors located in the rectum; (E-H) subgroup analysis in older patients. OS, overall survival; CSS, cancer specific survival; y, years; ER, endoscopic resection; CRT, chemoradiotherapy.

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suggesting that ER is an ideal choice for early-stage CRC patients. Through subgroup analysis, ER + CRT treatment was more beneficial to patients of older age and patients whose tumors were located in the rectum, with a significantly better OS and CSS. A multicenter randomized trial performed by Borstlap *et al.* suggested adjuvant CRT is an oncochemically safe treatment option in patients with high-risk T1 CRC and that CRT is expected to substantially improve morbidity, function and quality of life compared to radical surgery (18). Another study has shown that adjuvant (chemo)radiotherapy after local resection has the potential to decrease the risk of local recurrence by sterilizing occult metastatic lymph nodes and residual cancer cells within the rectal wall at the time of local resection (19). Therefore, adjuvant CRT after ER might be an alternative to radical surgery for these patients.

Despite numerous studies, it remains unclear why colon cancer outcomes differ from those of the rectum (20-22). In clinical practice, the R0 resection rate and en bloc resection rate are easier to achieve in the rectum than in the colon (21). The en bloc resection rates in the colon and rectum were 78% and 87%, respectively (22). The post-ER complication rate was also lower in the rectum than in the colon. There is a wider field of resection in the colon than in the rectum, which may result in greater damage to the large intestine and thus negatively impact survival in colon cancer patients after resection (23). Anatomically, the colon mesentery may involve a more complex lymphatic system, leading to an enhanced immune response and an increased number of lymph nodes examined for colon (24).

SEER data provide several advantages, including the ability to report survival outcomes and to provide evidence to compare outcomes on the basis of large sample sizes. To minimize the interference caused by baseline differences, we used PSM to achieve balanced cohorts and OS and CSS as our primary treatment outcomes. In the case of retrospective cohort studies, selection biases are inherent. This limits the interpretation of our results. These problems could not be resolved by PSM, multivariate adjustment, nor subgroup analysis.

Conclusions

According to this real-world retrospective study, OS and CSS rates are similar between ER and ER + CRT groups. Older patients and rectal cancer patients benefit from ER + CRT. Further prospective randomized clinical trials are needed to evaluate and validate these results.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1411/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1411/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1411/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval and informed consent were not required in the current study because SEER research data are publicly available and all patient data are de-identified.

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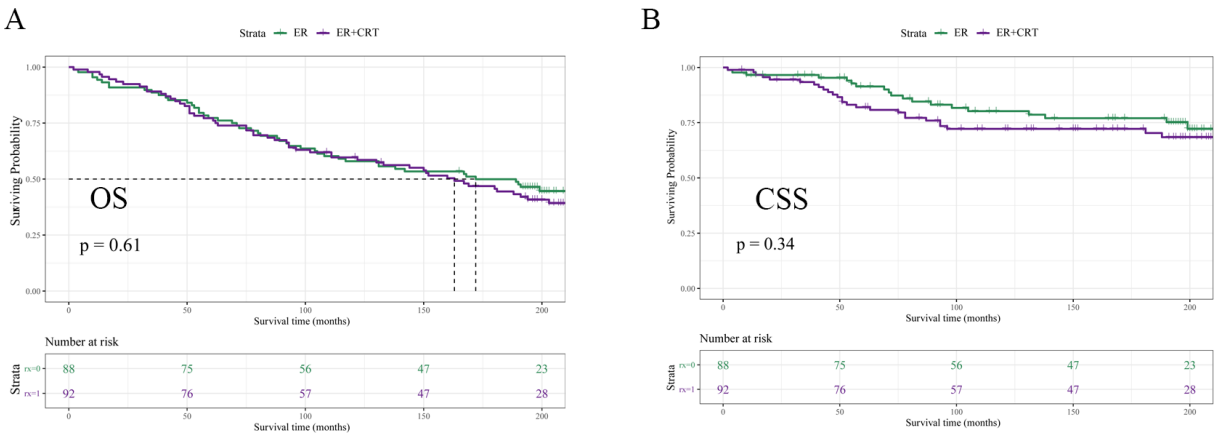

Figure S1 The survival rates of the two groups in rectal cancer patients after PSM. (A) The OS rates of ER and ER + CRT groups (P=0.61); (B) the CSS rates of ER and ER + CRT groups (P=0.34). OS, overall survival; CSS, cancer specific survival; PSM, propensity score matching; ER, endoscopic resection; CRT, chemoradiotherapy; rx, treatment.

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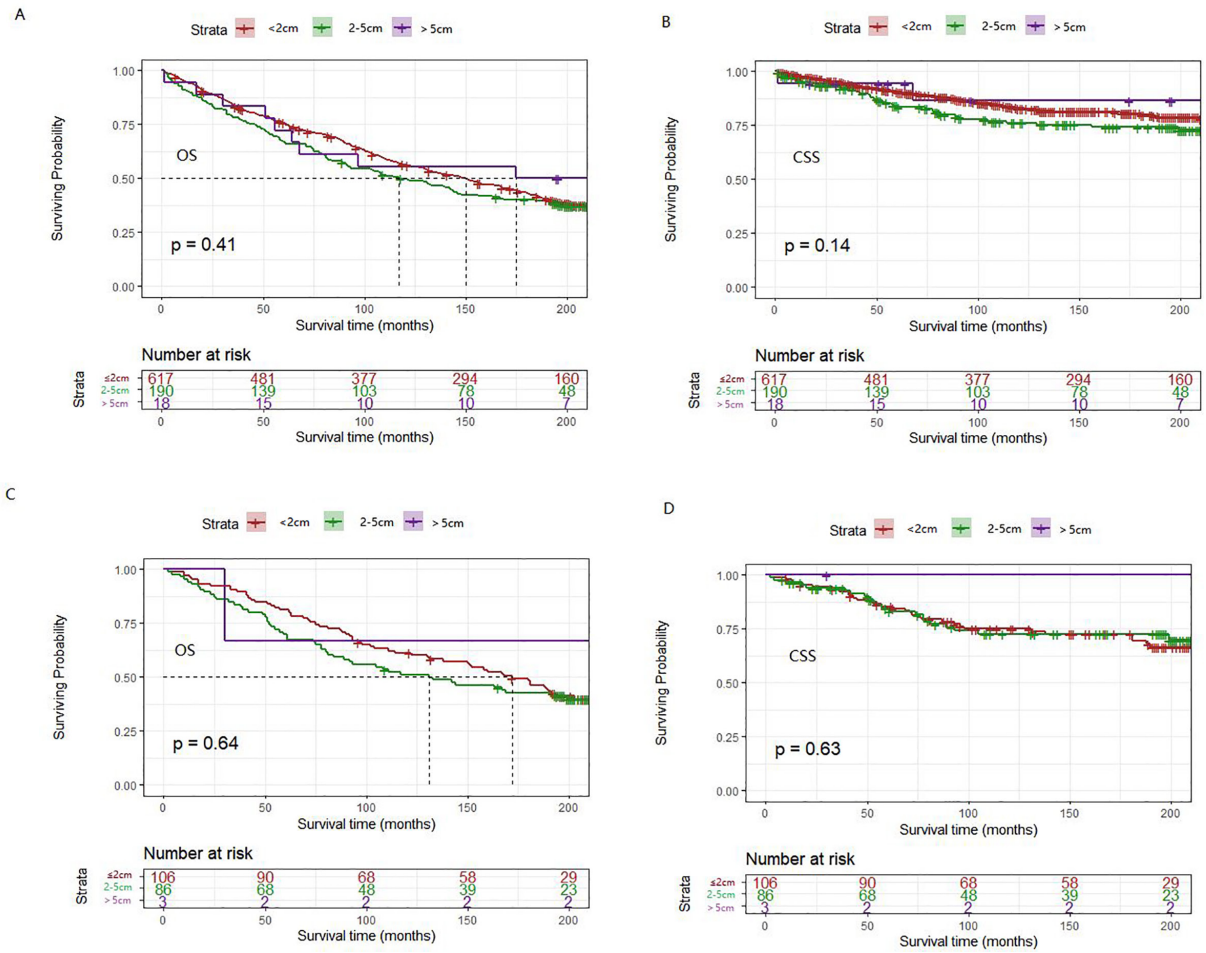

Figure S2 Subgroup analysis considering tumor size. (A) The OS rate of ER + CRT *vs.* ER group before PSM (P=0.41); (B) the CSS rate of ER + CRT *vs.* ER group before PSM (P=0.14); (C) the OS rate of ER + CRT *vs.* ER group after PSM (P=0.64); (D) the CSS rate of ER + CRT *vs.* ER group after PSM (P=0.63). OS, overall survival; CSS, cancer specific survival; ER, endoscopic resection; CRT, chemoradiotherapy; PSM, propensity score matching.

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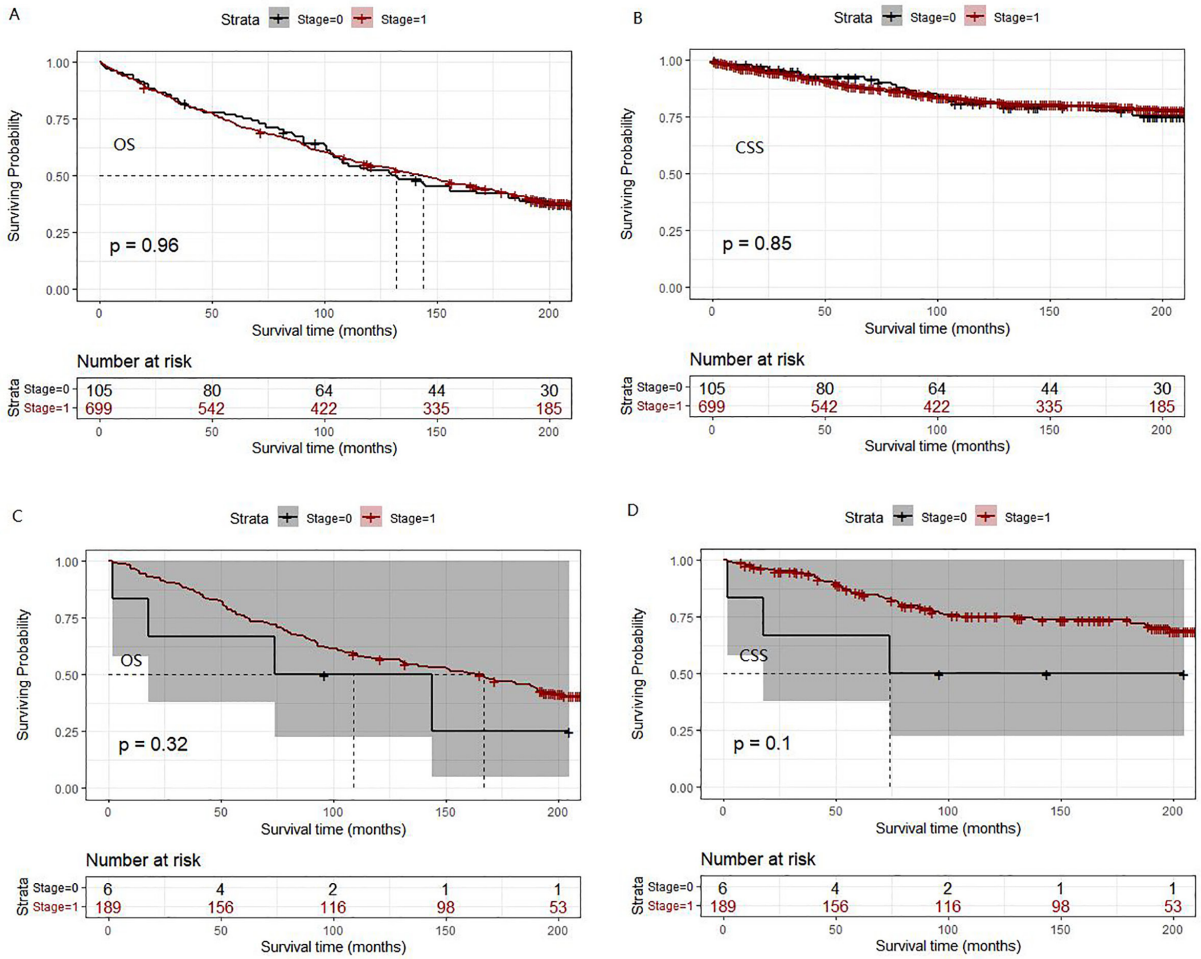

Figure S3 Subgroup analysis considering tumor stage. (A) The OS rate of ER + CRT *vs.* ER group before PSM (P=0.96); (B) the CSS rate of ER + CRT *vs.* ER group before PSM (P=0.85); (C) the OS rate of ER + CRT *vs.* ER group after PSM (P=0.32); (D) the CSS rate of ER + CRT *vs.* ER group after PSM (P=0.10). OS, overall survival; CSS, cancer specific survival; ER, endoscopic resection; CRT, chemoradiotherapy; PSM, propensity score matching.

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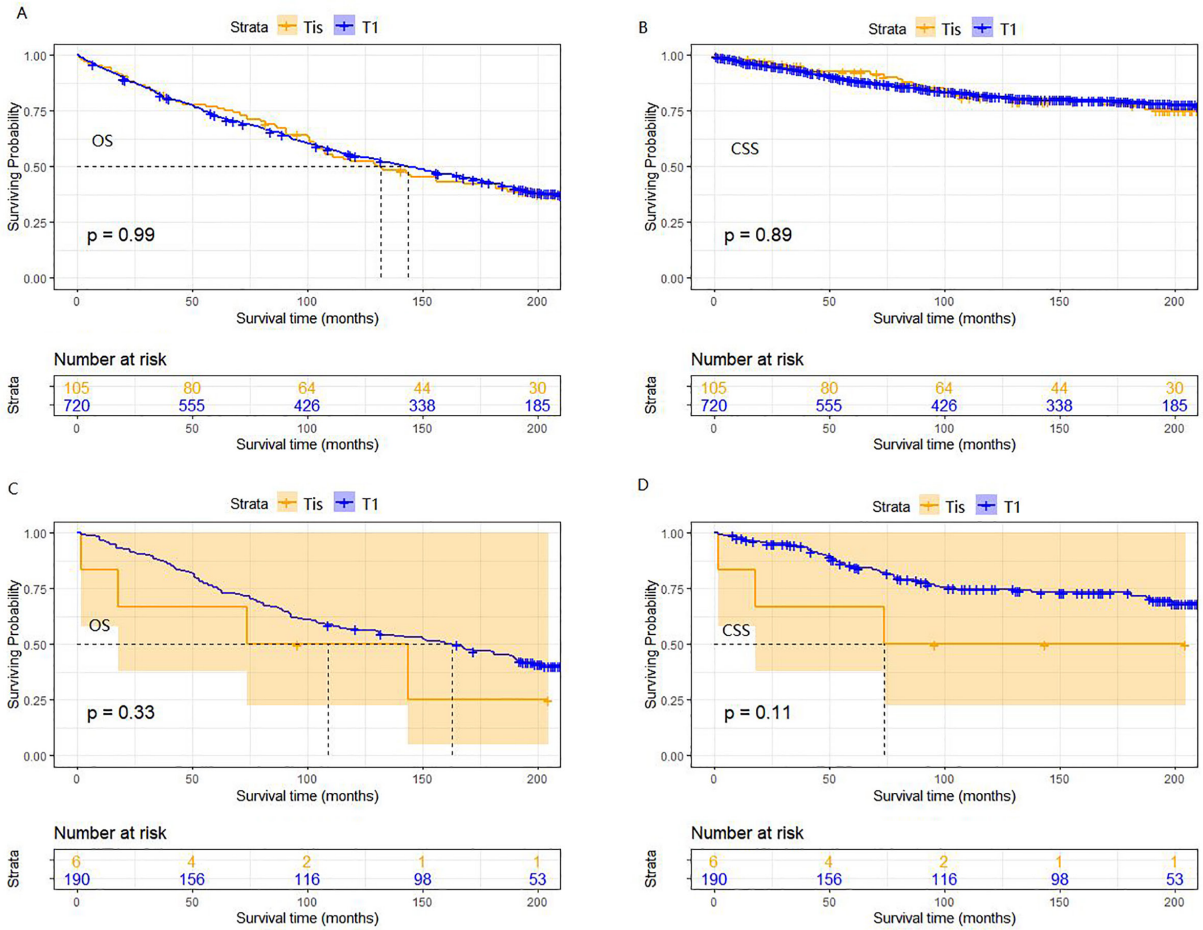

Figure S4 Subgroup analysis considering invasion depth. (A) The OS rate of ER + CRT *vs.* ER group before PSM (P=0.99); (B) the CSS rate of ER + CRT *vs.* ER group before PSM (P=0.89); (C) the OS rate of ER + CRT *vs.* ER group after PSM (P=0.33); (D) the CSS rate of ER + CRT *vs.* ER group after PSM (P=0.11). OS, overall survival; CSS, cancer specific survival; ER, endoscopic resection; CRT, chemoradiotherapy; PSM, propensity score matching.

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