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Efficacy of Neoadjuvant Therapy in Improving Long-Term Survival of Patients With Resectable Rectal Cancer: A Meta-Analysis

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Abstract

Background: The impact of neoadjuvant therapy on the long-term prognosis of patients with resectable rectal cancer is controversial. This study aimed to explore the effect of neoadjuvant therapy on the long-term prognosis of patients with resectable rectal cancer.

Methods: Four major databases (PubMed, Web of Science, Embase, Cochrane library) were searched to find relevant articles published between January 2000 and July 2020. The main outcome indicators were the 5-year overall survival (OS) and disease-free survival (DFS).

Results: Compared with upfront surgery, our meta-analysis showed that 5-year OS (HR: 0.84, 95% CI: 0.78-0.91) and DFS (HR: 0.91, 95% CI: 0.87-0.95) were prolonged for patients with resectable rectal cancer after receiving neoadjuvant therapy. The results of subgroup analysis suggested that both neoadjuvant short-course radiotherapy (SCRT) and neoadjuvant chemo-radiotherapy (CRT) could improve the 5-year OS and DFS. The 5-year OS and DFS of patients with stage □-□ rectal cancer increased significantly and the improvement of 5-year OS and DFS could also be observed in mid/low rectal cancer.

Conclusion: Neoadjuvant therapy could improve the long-term survival of patients with mid/low rectal cancer in stage □-□. For the treatment, neoadjuvant SCRT and neoadjuvant CRT were recommended.

1. Background

According to the global cancer statistics of 2018, the incidence of colorectal cancer was as high as 10.2%, ranking third among all cancers and second only to lung cancer in terms of mortality [1]. Moreover, in the treatment of patients with rectal cancer, the patients experience the loss of the rectal sphincter, intestinal dysfunction, urinary and reproductive system dysfunction, which seriously affect the life quality [2, 3]. Over the past several decades, researchers have explored multidisciplinary approaches for the treatment of patients with primary rectal cancer to reduce morbidity and mortality and improve the quality of life [4].

In the application of neoadjuvant short-course radiotherapy (SCRT), the Swedish rectal cancer trial showed that neoadjuvant SCRT could improve the survival rate of patients and reduce the risk of local recurrence (LR) [5]. However, studies in the Netherlands and Germany found that the combination of neoadjuvant SCRT and surgery had no survival benefit, although it could reduce the risk of LR [6, 7]. However, the surgery in the Swedish study did not apply the total mesorectal excision (TME) unlike the other two used, but the reason for the inconsistent conclusions is still unclear [8]. Preoperative radiotherapy combined with chemotherapy has also been applied in the treatment of resectable rectal cancer; studies have shown that this combined treatment could effectively reduce the size of advanced tumors, increase the R0 resection rate, reduce the LR and improve the long-term survival rate [9–11]. Unfortunately, some studies suggested that neoadjuvant chemo-radiotherapy (CRT) combined with TME, a standard treatment for locally advanced rectal cancer, did not benefit patients for long-term survival [12, 13] and even worsened the quality of life to these patients [14]; though they believed that this therapy was related to the better local control [12]. Currently, neoadjuvant chemotherapy has not been used commonly and related studies are rare. In addition, concerning tumor location, some studies have demonstrated that preoperative radiotherapy did not significantly improve the local control of patients with upper rectal cancer [5], yet the debate on this view has never stopped [15].

Generally, meta-analysis has supported the conclusion that neoadjuvant therapy can improve the local control of rectal cancer [16]. However, it is not clear whether neoadjuvant therapy can improve the overall survival (OS) and disease-free survival (DFS) of patients with resectable rectal cancer; especially the long-term efficacy. This article adressed various neoadjuvant treatment regimens and comprehensively analyzed the influence of multiple factors on the efficacy of neoadjuvant treatment in patients with resectable rectal cancer.

2. Methods

2.1 Search strategy

A systematic search was performed in PubMed, Web of Science, Embase, and Cochrane library to find English clinical studies related to the role of neoadjuvant treatment in resectable rectal cancer, which was published between January 2000 and July 2020. This search used the following as keywords: “Rectal neoplasms”, “neoadjuvant therapy”, “neoadjuvant chemo-radiotherapy”, “neoadjuvant radiotherapy”, “neoadjuvant chemotherapy”, “preoperative treatment”, “preoperative radiotherapy”, “preoperative chemo-radiotherapy” and “preoperative chemotherapy”. Furthermore, related studies appearing in references were also searched to avoid omissions. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was guided this meta-analysis [17].

2.2 Study selection

Inclusion criteria: (1) The patients with resectable rectal cancer. (2) The article compared the patients undergoing neoadjuvant therapy with the patients undergoing upfront surgery. (3) Long-term prognostic outcomes (OS and/or DFS) should be reported in the study. (4) The follow-up

time required more than five years.

Exclusion criteria: (1) Patients who had palliative treatment or distant metastases. (2) The study included not only patients with rectal cancer but also patients with other malignant tumors (such as colon cancer). (3) Data was not extractable. (4) The baseline characteristics of patients between groups were quite different and there was less comparable. (5) Other forms of treatment (e.g., hyperthermia and intraoperative radiotherapy) occurred during surgical treatment. (6) If there were duplicate publications for the same trial, the most appropriate or updated version was included in the final analysis.

2.3 Date extraction and quality assessment

The extraction and quality assessment of data of the studies were independently completed and checked by two researchers, and any inconsistencies were resolved by the third researcher to avoid bias. The information extracted from each study included not only baseline information such as author, year of publication, country, tumor location, tumor staging, number of patients, treatment regimen, type of study, age, and follow-up time, but also the prognostic outcomes of the studies (OS and DFS).

In terms of quality assessment, the Cochrane Collaboration’s tool was used to evaluate randomized controlled trials (RCTs) from the six aspects of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and free of other bias. The level of risk of bias was mainly distinguished from “high risk”, “low risk”, and “unclear risk”. Other observational studies (OBSs) were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). After that, higher-quality articles were selected for inclusion in this meta-analysis.

2.4 Statistical analysis

Hazard ratios (HR) as well as 95% confidence intervals (CI) were utilized to evaluate the long-term prognosis between the neoadjuvant group and the control group. Cochran Chi-square test and I^2 were used to examine heterogeneity. Subgroup analysis was performed according to the heterogeneity of the statistical results. Moreover, a random-effect model was applied, due to the diversity of neoadjuvant treatments, to help increase reliability. The Begg’s test and Egger’s test were used to appraise publication bias. $P < 0.05$ was considered statistically significant. Sensitivity analysis was applied to assess the stability of the results. Stata 12.0 Software was a vital tool for all statistical analysis.

3. Results

3.1 Literature search

According to the keywords and search strategy, 37164 citations were obtained from the four major databases of PubMed, Web of Science, Embase, Cochrane library, and other channels. There were 8523 remaining after excluding duplicate studies. Among the 8523 citations, 8292 studies were excluded by the title and abstract. After browsing the full text of the remaining 231 studies, 187 articles did not meet the criteria of our research. The reasons were as follows: 5 articles were non-original articles, 3 were duplicate reports, 125 lacked applicable date, 31 had no comparable results, 20 did not include long-term outcome, and 3 had palliative treatment. After several levels of screening, 5 RCTs and 39 OBSs were ultimately included in this meta-analysis [5–7, 18–58]. Figure 1 shows the flow diagram of the screening.

3.2 Characteristics of included studies

A total of 44 studies with long-term results (five years and more) were picked, spanning January 2000 to July 2020; comprising 71834 patients from Asia, Europe, and America (41490 cases in the neoadjuvant treatment group, 30344 cases in the control group). Their median age at diagnosis was mainly > 50 years old. Two studies recorded 7-year outcomes, one recorded 10-year outcomes, and one recorded 13-year outcomes, the remaining 40 articles described the outcome of 5 years. Twenty two articles describedg mid/low rectal cancer, and 3 articles described upper rectal cancer. Most tumors were staged [illegible]-[illegible]. Magnetic resonance imaging (MRI) and endorectal ultrasound (ERUS) were common preoperative staging methods. Neoadjuvant treatment was divided into neoadjuvant radiotherapy (RT) which was other than SCRT, neoadjuvant SCRT, neoadjuvant chemotherapy, or neoadjuvant CRT. In this meta-analysis, the most universal neoadjuvant regimen was neoadjuvant CRT, whereas neoadjuvant chemotherapy was the least used, and TME was the commonly used surgical method. Regarding the adjuvant treatment, most studies comprehensively considered the postoperative situation of patients, clinical guidelines, and the judgment of doctors to make the decision. More specific information is provided in Table 1 and Supplementary Table 1. Quality assessment was conducted on all articles (Supplementary Table 2).

Table 1
Characteristics of all the studies included in the meta-analysis.

Author	Year	Country	Tumor		Patients number		Regimen		Study
			Distance from the anal verge	AJCC/ UICC	Experiment	Control	Experiment	Control	
Tabchouri	2020	France	10-15cm	cT3-T4	48	79	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Sorrentino	2019	Italy	NA	cT3N0	42	42	CRT + surgery + chemotherapy	Surgery + CRT /chemotherapy	OBSs*
de Camargo	2020	USA	NA	cT3N0	94	33	CRT + surgery + RT/chemotherapy	Surgery + RT /chemotherapy	OBSs
Wang	2018	China	≤ 10 cm	cT3-T4 or N+	90	94	CRT + surgery + Chemotherapy	Surgery+ chemotherapy	RCT
Räsänen	2019	Finland	NA	pT3 N1-N2	94	57	SCRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Jawitz	2019	USA	NA	cT2N0	2456	9565	CRT + surgery + RT/CRT /chemotherapy	Surgery + RT/CRT /chemotherapy	OBSs*
Rades	2018	Germany	10-15cm	Stage [illegible]-[illegible]	52	208	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Sprenger	2018	Germany	≤ 16 cm	cT3-T4 or N+	406	145	CRT + surgery	Surgery	RCT
Sun	2017	USA	NA	cStage [illegible]-[illegible]	890	9714	Chemotherapy + surgery+ chemotherapy	Surgery+ chemotherapy	OBSs
					1170		RT + surgery + chemotherapy	Surgery+ chemotherapy	
					21204		CRT + surgery + chemotherapy	Surgery+ chemotherapy	
Zhang	2017	China	≤ 12 cm	cStage [illegible]-[illegible]	101	101	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs*
Cho	2017	Korea	≤ 10 cm	T3ab and clear MRF	70	70	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs*
Sun	2017	China	≤ 12 cm	cT3-T4 or N+	375	375	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs*
Nagasaki	2017	Japan	≤ 5 cm	cT3-T4	30	43	CRT + surgery + chemotherapy	Surgery + RT /chemotherapy	OBSs
Joye	2016	Belgium	NA	cStage [illegible]-[illegible]	3022	1354	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs

*A Propensity Score-Matched Analysis; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; NA, Not available; RCT, Randomized controlled trial; SCRT, Short course radiotherapy; CRT, Chemo-radiotherapy; RT, Radiotherapy (other than SCRT); OBSs, Observational studies; MRF, Mesorectal fascia invasion.

Author	Year	Country	Tumor		Patients number		Regimen		Study
			Distance from the anal verge	AJCC/ UICC	Experiment	Control	Experiment	Control	
					797		RT + surgery + chemotherapy	Surgery+ chemotherapy	
Sineshaw	2016	USA	NA	Stage □-□	NA	NA	CRT + surgery	Surgery	OBSs
Li	2016	China	NA	Stage □-□	87	204	RT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
					102		Chemotherapy + surgery+ chemotherapy		
					81		CRT + surgery + chemotherapy		
van Erning	2015	The Netherlands	NA	pStage □	537	164	SCRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
					128	164	CRT + surgery + chemotherapy	Surgery+ chemotherapy	
Kulu	2016	Germany	≤ 12 cm	Stage □-□	212	112	RT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
					130		CRT + surgery + chemotherapy	Surgery+ chemotherapy	
Hwang	2015	South Korea	≤ 10 cm	cStage □-□	500	394	CRT + surgery + chemotherapy	Surgery + RT /chemotherapy	OBSs
Williamson	2014	UK	≤ 10 cm	cStage □-□	110	156	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Saito	2014	Japan	≤ 5 cm	cT3-T4	40	115	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Maas	2013	The Netherlands	NA	pT2-T3 N0-N2	346	296	SCRT + surgery	Surgery	OBSs
Lange	2013	USA	≤ 12 cm	Stage □-□	128	227	CRT + surgery + RT/CRT /chemotherapy	Surgery + RT/CRT /chemotherapy	OBSs
					8		RT + surgery + RT/CRT /chemotherapy	Surgery + RT/CRT /chemotherapy	
					5		Chemotherapy + surgery + RT/CRT/chemotherapy	Surgery + RT/CRT /chemotherapy	
Zhan	2013	China	≤ 10 cm	T3-T4 or N+	101	162	RT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs

*A Propensity Score-Matched Analysis; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; NA, Not available; RCT, Randomized controlled trial; SCRT, Short course radiotherapy; CRT, Chemo-radiotherapy; RT, Radiotherapy (other than SCRT); OBSs, Observational studies; MRF, Mesorectal fascia invasion.

Author	Year	Country	Tumor		Patients number		Regimen		Study
			Distance from the anal verge	AJCC/ UICC	Experiment	Control	Experiment	Control	
Shapiro	2013	USA	< 10 cm	uT3	289	95	CRT + surgery	Surgery	OBSs
Bębenek	2012	Poland	≤ 6 cm	Stage [illegible]-[illegible]	154	44	CRT/SCRT + surgery	Surgery	OBSs
Spitale	2012	Switzerland	NA	T3-T4 N1-N2	206	178	CRT/RT + surgery + chemotherapy	Surgery + RT /chemotherapy	OBSs
Tiefenthal	2011	Sweden	NA	Stage [illegible]-[illegible]	2804	1382	SCRT + surgery	Surgery	OBSs
Kao	2010	China	≤ 10 cm	cT3-T4 or N+	69	67	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Ferenschild	2009	The Netherlands	NA	pT2-T3 N0	31	72	SCRT + surgery	Surgery	OBSs
den Dulk	2008	The Netherlands	NA	pT1-T3	885	1537	RT + surgery	Surgery	OBSs
					67	1537	CRT + surgery	Surgery	
					44	54	RT + surgery + chemotherapy	Surgery+ chemotherapy	
Cheung	2009	China	≤ 12 cm	T3-T4 or N+	50	116	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Huh	2008	Korea	≤ 6 cm	cT2-T4 or N+	43	44	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Peeters	2007	The Netherlands	≤ 15 cm	NA	897	908	SCRT + surgery	Surgery	RCT
Tsujinaka	2008	Japan	≤ 5 cm	T3-T4	50	40	RT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Folkesson	2005	Sweden	NA	Stage [illegible]-[illegible]	454	454	SCRT + surgery	Surgery	RCT
Delaney	2002	USA	≤ 8 cm	pT3	167	92	RT + surgery	Surgery	OBSs
Watanabe	2002	Japan	≤ 5 cm	NA	78	37	RT + surgery	Surgery	OBSs
Read	2001	USA	NA	Stage [illegible]-[illegible]	135	17	RT + surgery	Surgery	OBSs
Fucini	2010	Italy	≤ 10 cm	T3	47	33	CRT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Han	2016	South Korea	NA	NA	439	411	CRT + surgery	Surgery	OBSs
					240	247			
Laurent	2006	France	≤ 15 cm	Stage [illegible]-[illegible]	202	98	RT + surgery + chemotherapy	Surgery+ chemotherapy	OBSs
Allaix	2012	Italy	≤ 10 cm	T2N0	9	32	RT + surgery	Surgery	OBSs
Sebag-Montefiore	2009	UK	≤ 15 cm	NA	674	676	SCRT + surgery	Surgery + selective CRT	RCT

*A Propensity Score-Matched Analysis; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; NA, Not available; RCT, Randomized controlled trial; SCRT, Short course radiotherapy; CRT, Chemo-radiotherapy; RT, Radiotherapy (other than SCRT); OBSs, Observational studies; MRF, Mesorectal fascia invasion.

3.3 Effect of neoadjuvant therapy on 5-year OS

In the cohort of this study, a total of 39 studies mentioned the long-term OS. Compared with the control group, the neoadjuvant treatment group had a significant survival benefit (HR: 0.84, 95% Cl: 0.78–0.91, $p < 0.001$; Fig. 2).

Considering the obvious heterogeneity ($I^2 = 92.6\%$), the subgroup analysis based on the type of study, tumor location, region, the neoadjuvant regimen, and tumor staging were conducted. The results of the subgroup analysis showed that neoadjuvant treatment was beneficial to 5-year OS for both the RCTs and the OBSs. For mid/low rectal cancer, neoadjuvant treatment tended to increase in 5-year OS (HR: 0.90, 95% Cl: 0.85–0.95). On the contrary, this benefit did not exist in upper rectal cancer (HR: 0.95, 95% Cl: 0.87–1.02). Neoadjuvant treatment was effective for the 5-year OS of patients in all compared regions when comparing the 5-year OS of patients in different regions (Asia, Europe, America). Among them, patients in Asia seemed to have better efficacy (HR: 0.75, 95% Cl: 0.56–0.94), patients in Europe (HR: 0.91, 95% Cl: 0.86–0.95) and America (HR: 0.88, 95% Cl: 0.76–0.99) seemed to have limited benefit. Additionally, different neoadjuvant treatments had different effects on survival. According to neoadjuvant therapy, among the 44 articles included, there were 7 for neoadjuvant SCRT, 24 for neoadjuvant CRT, 13 for neoadjuvant RT, and 3 for neoadjuvant chemotherapy. Both neoadjuvant SCRT (HR: 0.84, 95% Cl: 0.78–0.90) and neoadjuvant CRT (HR: 0.85, 95% Cl: 0.77–0.94) could improve 5-year OS, whereas neoadjuvant chemotherapy (HR: 0.80, 95% Cl: 0.54–1.05) and neoadjuvant RT (HR: 0.83, 95% Cl: 0.65–1.02) showed no survival benefits. The 5-year OS of stage �-� patients undergoing neoadjuvant treatment was significantly higher than that of the control group (HR: 0.81, 95% Cl: 0.72–0.91). Details are showed in Table 2.

Table 2
Subgroup analysis of the survival.

	No. of studies	HR	95%CI	Heterogeneity (I^2) (%)
5-year overall survival (OS)				
RCT	5	0.88	0.79–0.97	0
OBSs	34	0.84	0.77–0.91	93.3
Upper rectal cancer	3	0.95	0.87–1.02	0
Mid/low rectal cancer	20	0.90	0.85–0.95	65.5
Asia	13	0.75	0.56–0.94	93.1
Europe	19	0.91	0.86–0.95	69.3
America	7	0.88	0.76–0.99	91.3
Neoadjuvant SCRT	7	0.84	0.78–0.90	0
Neoadjuvant CRT	24	0.85	0.77–0.94	93.7
Neoadjuvant RT	13	0.83	0.65–1.02	95.0
Neoadjuvant chemotherapy	3	0.80	0.54–1.05	48.1
Stage �-�	25	0.81	0.72–0.91	95.1
5-year disease-free survival (DFS)				
OBSs	20	0.92	0.88–0.96	74.1
Mid/low rectal cancer	14	0.90	0.83–0.97	74.3
Asia	12	0.84	0.71–0.96	81.6
Europe	8	0.95	0.91-1.00	53.5
America	2	1.00	0.99–1.02	0
Neoadjuvant SCRT	3	0.84	0.75–0.92	0
Neoadjuvant CRT	15	0.96	0.91-1.00	76.6
Neoadjuvant RT	7	0.83	0.75–0.91	0
Stage �-�	16	0.94	0.90–0.98	70.0

HR, Hazard ratio; RCT, Randomized controlled trial; OBSs, Observational studies; SCRT, Short course radiotherapy; CRT, Chemo-radiotherapy; RT, Radiotherapy (other than SCRT).

3.4 Effect of neoadjuvant therapy on 5-year DFS

Long-term DFS was mentioned in 22 studies among the included articles. The neoadjuvant treatment group had better long-term DFS than the control group (HR: 0.91, 95% CI: 0.87–0.95, $p < 0.001$; Fig. 3).

Owing to the obvious heterogeneity ($I^2 = 74.2\%$), in the subgroup analysis, 20 OBSs had shown that neoadjuvant therapy could increase 5-year DFS. Compared with the control group, the 5-year DFS increased significantly in the neoadjuvant treatment group of patients with mid/low rectal cancer (HR: 0.90, 95% CI: 0.83–0.97) and stage �-� rectal cancer (HR: 0.94, 95% CI: 0.90–0.98). The 5-year DFS of patients in Asia (HR: 0.84, 95% CI: 0.71–0.96) and Europe (HR: 0.95, 95% CI: 0.91-1.00) improved under neoadjuvant treatment, and patients in Asia seemed to benefit more. For America, neoadjuvant treatment was of little significance for 5-year DFS (HR: 1.00, 95% CI: 0.99–1.02). However, only 2 articles were included in the subgroup analysis of 5-year DFS in America, 8 in Europe, and 12 in Asia. In terms of neoadjuvant treatment, neoadjuvant SCRT, CRT, and RT could improve 5-year DFS (Table 2).

3.5 Publication bias and sensitivity analysis

The Begg's and Egger's tests were used to perform a publication bias test on the 5-year OS of the included articles and no significant publication bias was found (Egger's test $p = 0.105$, Begg's test $p = 0.871$; Supplementary Fig. 1). When performing sensitivity analysis, the

results of each group were sequentially removed, and the results were stable (Supplementary Fig. 2).

4. Discussion

The prevalence of rectal cancer is relatively high. Additionally, there were predictions that the prevalence of rectal cancer may deteriorate [4], and even tend to among a younger population [59]. Despite decades of exploration, in terms of treatment options, researchers still hold mixed opinions on the efficacy of neoadjuvant therapy that has been widely used. For example, national guidelines in the United States have supported the use of neoadjuvant CRT for all patients with stage �-� rectal cancer since 2002 [60]. However, many researchers think that this treatment option is no different from upfront surgery in the survival rate of patients [57].

The main outcome indicators of our analysis were the 5-year OS and DFS. The results demonstrated that neoadjuvant therapy was effective in improving the 5-year OS and DFS of patients, which was consistent with the conclusions of Nagasaki *et al*. [37] and Kao *et al*. [31]. A subgroup analysis was conducted to increase credibility, considering the heterogeneity of the results. In terms of the type of studies, further research showed that both RCTs and OBSs neoadjuvant therapy could improve the long-term OS as well as DFS of patients.

Focusing on neoadjuvant treatment regimens, neoadjuvant CRT was beneficial to improve the 5-year OS and DFS of the patients compared with the control group. Sun *et al*. [48] and Kao *et al*. [31] had the same conclusions. Interestingly, two RCTs (Wang *et al*. [53] and Sprenger *et al*. [46]) reached the opposite conclusions using TME. In our study, more OBSs were included, in which patients with lower age, lower tumor location, and better tolerance were more likely to receive neoadjuvant therapy [50]. For example, patients aged over 75 years had a higher risk of complications after radiation exposure[36] and were less likely to receive neoadjuvant CRT in OBSs. However, RCTs eliminated the differences between the groups of patients, which may be one of the reasons why neoadjuvant CRT had no benefit to survival in RCTs. Furthermore, the use of TME may also mask the survival benefits [39]. Therefore, a retrospective study deserved attention. The patients who participated in the study also used TME during surgery, but the conclusions indicated that neoadjuvant therapy could significantly improve the 5-year OS and DFS. Interestingly, the subjects of this study had rectal cancer with lymph node metastasis [37]. Therefore, we postulated that patients with lymph node metastasis were more likely to benefit from neoadjuvant therapy. The effect of neoadjuvant therapy may also be affected by circumferential resection margins (CRM) and extramural vascular invasion (EMVI). Studies have shown that positive CRM would indicate a high risk of recurrence [61]. The EMVI was also considered to be related to poor outcomes [4]. Therefore, subsequent studies may explore these factors to promote more selective and personalized treatment of patients with resectable rectal cancer.

Regarding the use of neoadjuvant SCRT, the results of our study and Folkesson *et al*. [5] supported the claim that neoadjuvant SCRT could achieve better long-term survival rates for patients with rectal cancer. Pettersson *et al*. [62] proposed that neoadjuvant SCRT could be used to treat patients who were intolerant to neoadjuvant CRT. However, the findings of Sebag-Montefiore *et al*. [7] and van Gijn *et al*. [63] did not support the above conclusion. The use of TME might be an important factor contributing to this result, which reduced the risk of LR and may make neoadjuvant SCRT less important in reducing the LR [64]. At the same time, TME could reduce CRM involvement and improve the survival rates of patients [47]. Hence, the survival benefits of neoadjuvant SCRT could not be reproduced in the above studies.

On the other hand, our data indicated that the neoadjuvant RT (other than neoadjuvant SCRT) did not bring benefits to the 5-year OS of patients (HR: 0.83, 95% CI: 0.65–1.02). Neoadjuvant RT may induce metastasis of molecules such as the vascular endothelial growth factor (VEGF) that stimulate angiogenesis, whose over-expression was associated with distant metastasis [65]. The high rate of distant metastasis was also an important factor in the increased mortality of patients receiving neoadjuvant therapy [47]. Additionally, adverse effects caused by neoadjuvant RT (such as anastomotic leakage, thrombocytopenia, leukopenia, poor wound healing and radiation proctitis, etc.) may not only affect the quality of life of patients but also indirectly reduced the life expectancy [14, 66, 67]. Although neoadjuvant RT could benefit long-term DFS (HR: 0.83, 95% CI: 0.75–0.91), the tumor-killing effect of neoadjuvant RT may be masked by its adverse effects and fail to improve 5-year OS.

The application of neoadjuvant chemotherapy in this study did not increase the long-term survival rate of patients compared with the control group. The impact of a small sample size should be considered. Currently, an RCT (NCT01515787) is exploring whether neoadjuvant chemotherapy could replace neoadjuvant CRT and effectively treat patients with stage �-� rectal cancer [68].

Regarding the staging of rectal cancer patients, the study demonstrated that neoadjuvant therapy was effective in improving the 5-year OS and DFS for patients with stage �-�, which was similar to the indications proposed in the NCCN guidelines [69].

In terms of tumor location, the data of our study showed that compared with the control group, patients with resectable mid/low rectal cancer had better 5-year OS and DFS after neoadjuvant therapy, whereas the resectable upper rectal cancer showed no benefit in the 5-year OS (HR: 0.95, 95% CI: 0.87–1.02). The conclusion that neoadjuvant CRT and neoadjuvant SCRT may not be suitable for the treatment of upper rectal cancer was consistent with the views of Tabchouri *et al*. [49] and Rades *et al*. [38]. The possible reason for this is that the location of mid/low rectal cancer was relatively fixed, whereas upper rectal cancer was more active and had poor therapeutic effect. However, the low number of

included articles was also a factor that should be considered. There were similar views in the ESMO clinical practice guidelines: If upper rectal cancers located above the peritoneal reflection failed to benefit from neoadjuvant SCRT or neoadjuvant CRT, treating them as colon cancer was recommended [4].

As far as the included regions were concerned, patients could achieve 5-year OS benefits with the effect of neoadjuvant therapy, and patients in Asia seemed to benefit more. As for 5-year DFS, neoadjuvant therapy could improve the DFS of Asian and European patients to a limited extent, whereas patients in America had no improvement in DFS. Black race was one of the high-risk factors for poor prognosis [43]. Considering that the proportion of blacks in America was higher than in other regions may be a reason why there was no survival benefit for patients in America in our study. There were only two articles from America among the articles included in this subgroup analysis for DFS.

This study had some limitations: First, the OBSs were included in this meta-analysis, so the level of evidence inevitably decreased. Also, the diagnosis of clinical staging has not been standardized, and the preoperative staging methods were diverse. The difference in patient staging caused by preoperative staging methods made it difficult to specifically assess whether the conditions of patients were overestimated or underestimated. Analysis of some related factors affecting the prognosis of rectal cancer patients could not be performed due to lack of data, such as gender and gene type. Some studies suggested that the narrower pelvis of men would affect the prognosis of men with rectal cancer [50]. Also, the gene type of the tumor was an important factor affecting the prognosis of patients [70]. Relevant subgroup analysis was not conducted due to the small number of studies on early rectal cancer. However, it was gratifying that we analyzed the efficacy of various neoadjuvant treatments on different locations and stages of rectal cancer from multiple angles, explored its impact on the long-term survival rate of patients with resectable rectal cancer, and provided new ideas for further research on resectable rectal cancer.

5. Conclusion

The study further confirmed the efficacy of neoadjuvant therapy in stage [illegible]-[illegible] mid/low rectal cancer. Neoadjuvant SCRT and neoadjuvant CRT were also recommended. However, the conclusions of this study need to be confirmed using large multi-center RCTs.

Abbreviations

SCRT, Short-course radiotherapy; LR, local recurrence; TME, total mesorectal excision; CRT, Chemo-radiotherapy; RT, Radiotherapy (other than SCRT); OS, Overall survival; DFS, Disease-free survival; RCTs, randomized controlled trial; OBSs, Observational studies; NOS, Newcastle-Ottawa Quality Assessment Scale; HR, Hazard ratios; CI, Confidence intervals; MRI, Magnetic resonance imaging; ERUS, Endorectal ultrasound; CRM, Circumferential resection margins; EMVI, Extramural vascular invasion; VEGF, Vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Authors’ contributions

GC designed the research process. XLL and XYL searched the database for corresponding articles. RRF and DMG extracted useful information from the articles above. YZ and TY used statistical software for analysis. MTZ and YTS drafted the meta-analysis. YXG and CHL polished this article. All authors had read and approved the manuscript and ensured that this was the case.

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Figures

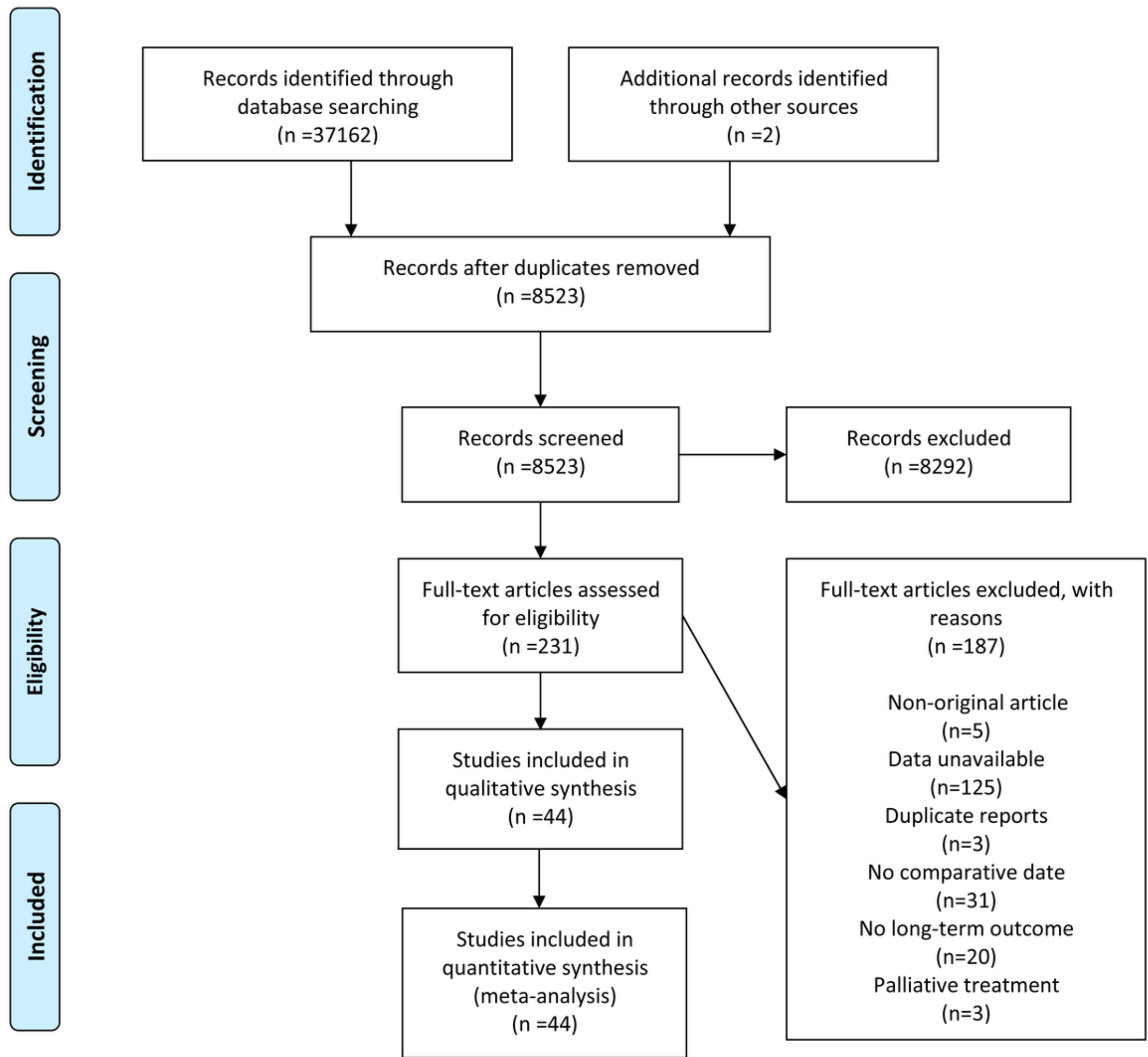

Figure 1

Flow diagram describing inclusion and exclusion criteria.

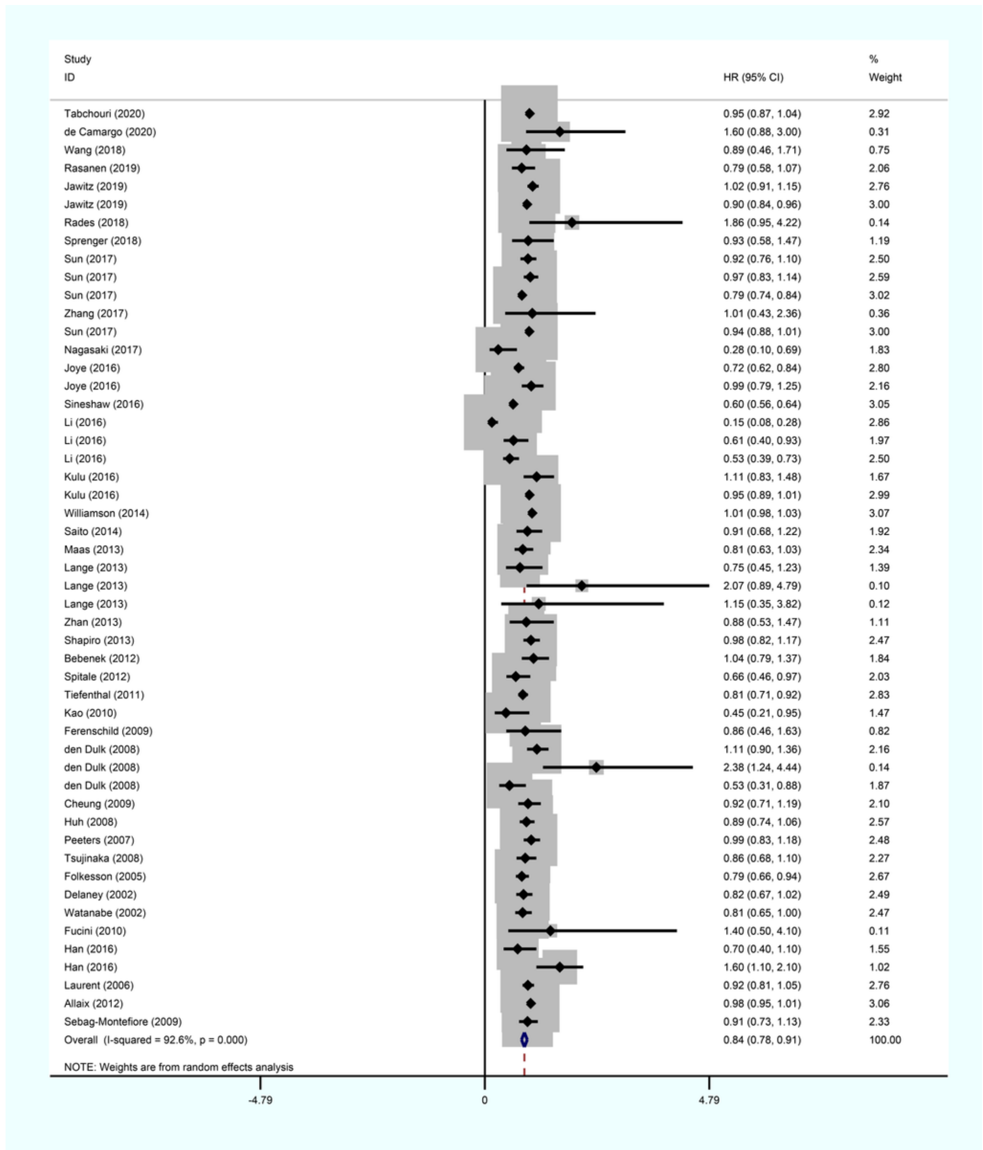

Figure 2

Forest plots of the 5-year overall survival for neoadjuvant treatment on resectable rectal cancer.

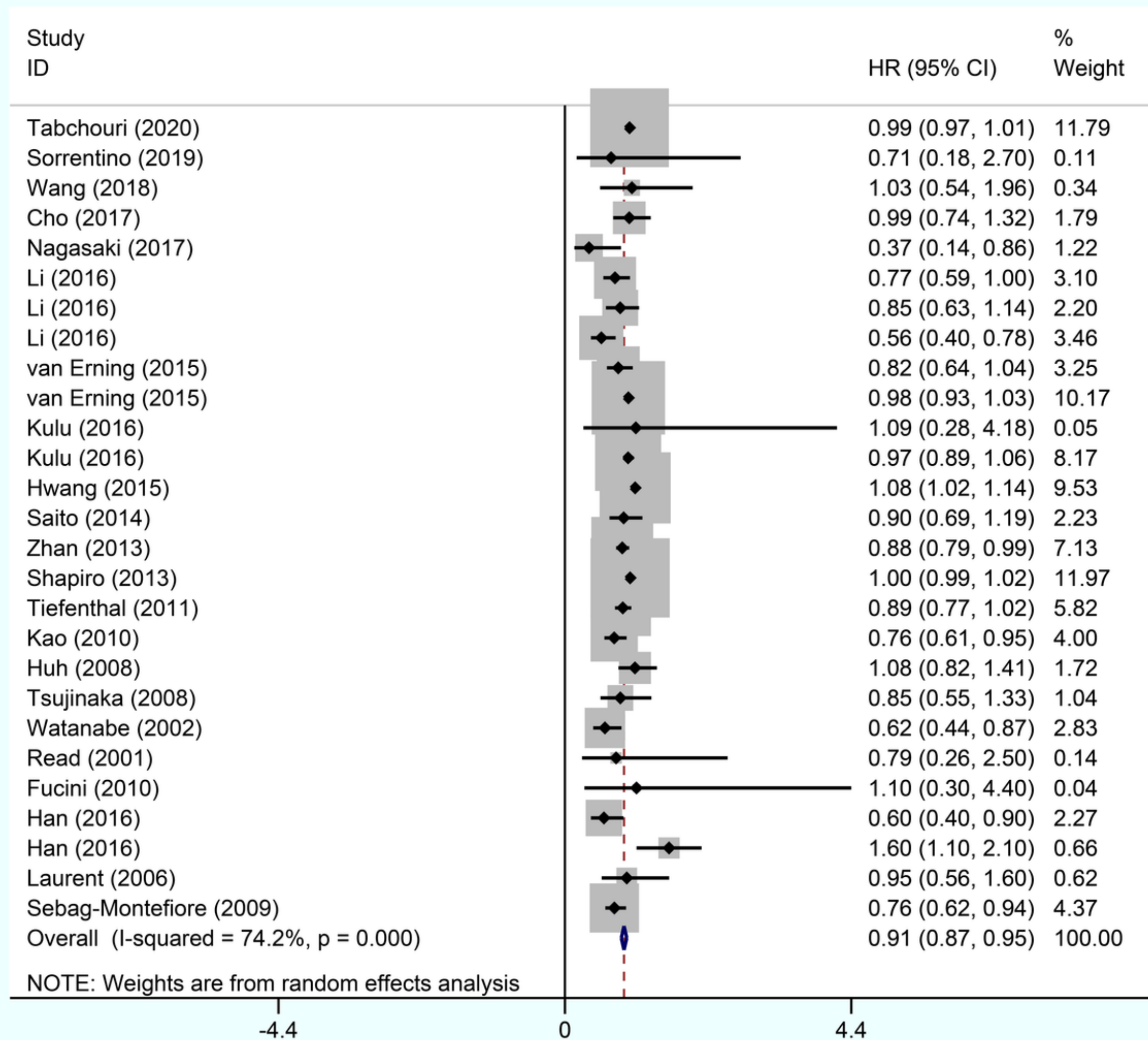

Figure 3

Forest plot of the 5-year disease-free survival for neoadjuvant treatment on resectable rectal cancer.

Supplementary Files

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