Oncoloଟ୍ରy Reviews

Check for updates

OPEN ACCESS

EDITED BY Francesk Mulita, General Hospital of Eastern Achaia- Unit of Aigio, Greece

REVIEWED BY Dimitrios Kehagias, University of Patras, Greece Spyros Papadoulas,

General University Hospital of Patras, Greece Andreas Antzoulas, General University Hospital of Patras, Greece

*CORRESPONDENCE Jianming He, ⊠ hjmlovelx@hotmail.com Zheng Zhi, ⊠ hbzyxyzz@163.com

 $^{\mathrm{t}}\mathrm{These}$ authors have contributed equally to this work

RECEIVED 28 January 2025 ACCEPTED 18 March 2025 PUBLISHED 01 May 2025

CITATION

Wang W, Zhao R, Liang X, Liu M, Bai H, Ge J, Yao B, Zhi Z and He J (2025) Efficacies of radiotherapy in rectal cancer patients treated with total mesorectal excision or other types of surgery: an updated meta-analysis. *Oncol. Rev.* 19:1567818. doi: 10.3389/or.2025.1567818

COPYRIGHT

© 2025 Wang, Zhao, Liang, Liu, Bai, Ge, Yao, Zhi and He. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Efficacies of radiotherapy in rectal cancer patients treated with total mesorectal excision or other types of surgery: an updated meta-analysis

Wenshu Wang^{1†}, Runyuan Zhao^{2†}, Xi Liang¹, Manjun Liu¹, Haiyan Bai¹, Jianli Ge¹, Binxi Yao¹, Zheng Zhi^{1*} and Jianming He^{1,3*}

¹Department of Radiotherapy, Hebei Province Hospital of Chinese Medicine, Hebei University of Chinese Medicine, Shijiazhuang, China, ²Department of Gastroenterology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, ³Key Laboratory of Integrated Chinese and Western Medicine for Gastroenterology Research (Hebei), Shijiazhuang, China

Background: An updated meta-analysis was conducted to evaluate the efficacy of radiotherapy in rectal cancer patients treated with total mesorectal excision (TME) or other types of surgery (non-TME-only).

Methods: The PubMed, Cochrane Library, and CNKI databases were searched. Data on overall survival (OS) were extracted.

Results: Hazard ratios (HRs) for OS associated with preoperative radiotherapy, preoperative long-course concurrent chemoradiotherapy (LCCRT), preoperative radiotherapy alone, and postoperative radiotherapy in patients treated with TME were 1.02 [95% CI: 0.92–1.14, P = 0.65], 1.04 [95% CI: 0.93–1.16, P = 0.47], 0.87 [95% CI: 0.61–1.25, P = 0.46], and 1.18 [95% CI: 0.91–1.52, P = 0.20], respectively. HRs for OS associated with preoperative radiotherapy, preoperative LCCRT, preoperative radiotherapy alone, preoperative long-course RT (LCRT), and preoperative short-course radiotherapy (SCRT) in patients treated with non-TME-only surgery were 0.85 [95% CI: 0.79–0.90, P < 0.0001], 0.77 [95% CI: 0.73–0.94, P = 0.009], 0.86 [95% CI: 0.77–0.91, P= <0.0001], 0.83 [95% CI: 0.73–0.95, P = 0.005], and 0.84 [95% CI: 0.77–0.91, P= <0.0001], respectively. The HR for postoperative radiotherapy in patients treated with non-TME-only surgery was 1.08 [95% CI: 0.84–1.39, P = 0.57].

Conclusion: Preoperative radiotherapy, regardless of the regimen, improves the OS in patients treated with non-TME-only surgery, but not in those treated with TME. Postoperative radiotherapy does not improve OS.

Advances in knowledge: This meta-analysis will serve as a reference for decision-making in multidisciplinary approaches for rectal cancer patients.

KEYWORDS

rectal cancer, radiotherapy, concurrent chemoradiotherapy, surgery, TME

1 Introduction

In 2022, an estimated 436,081 new cases of rectal cancer were reported in men and 293,621 in women, with 205,062 deaths in men and 138,699 in women (1). Its incidence is increasing in most developing countries, notably among young adults, and this may be partly attributed to lipid metabolism (1, 2, 3). Radiotherapy (RT) is widely accepted as an essential component of multidisciplinary treatment (MDT) for locally advanced rectal cancer (LARC), occurring in the mid and low rectum, primarily to reduce local recurrence (LR). However, MDT modalities vary considerably. Several RT regimens are available, such as concurrent chemoradiotherapy (CRT), sequential combinations of chemotherapy and RT (RT alone), long-course CRT (LCCRT), long-course RT (LCRT), and shortcourse RT (SCRT) (4, 5, 6).

Over the past decade, the standard treatment protocol for LARC consisted of neoadjuvant RT or CRT, followed by surgery and adjuvant systemic chemotherapy. Early response evaluation diffusion-weighted magnetic resonance using during neoadjuvant CRT has shown great promise in predicting the tumor response (7). Despite multiple efforts to potentiate preoperative CRT regimens, distant disease control and pathological complete response (pCR) remain suboptimal, with rates of approximately 25%-35% and 10%-15%, respectively (8, 9). To address the issues of distant metastasis and low pCR rates, total neoadjuvant therapy (TNT), which involves administering several cycles of chemotherapy either before RT/CRT (induction regimen) or after RT (consolidation regimen), has been tested and has shown promising results. TNT might improve metastasis-free survival, increase pCR and anal sphincter preservation rates, facilitate treatment adherence, and reduce toxicity (8, 10).

Recently, the supportive role of RT has been challenged. Total mesorectal excision (TME), the first-choice radical surgery, has been proposed as an alternative application to combined RT and surgery in patients with LARC, because TME significantly reduces LR without RT, thus questioning the necessity of RT either before or after surgery. van Gijn and Huh independently reported that the incidence of LR was less than 15% in the TME-alone group and preoperative RT did not improve overall survival (OS) (11, 12). Therefore, the impact of RT, particularly SCRT or postoperative RT, on OS remains a subject of debate. An updated meta-analysis was conducted to evaluate the efficacy of different RT regimens in patients with LARC treated with TME or other types of surgery (non-TME-only).

2 Materials and methods

2.1 Literature research

This study was designed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (3, 13). A systematic search of the PubMed, Cochrane Library, and CNKI databases was conducted to identify studies that examined the efficacy of RT in patients with rectal cancer. Articles written in either English or Chinese were included. The search strategy is detailed in the supplementary literature research.

2.2 Inclusion/exclusion criteria

The inclusion criteria were as follows: 1) patients: pathologically diagnosed rectal cancer at T1–T4N0–N + M0 stages. 2) Treatment: patients in the RT group underwent surgery followed by RT/CRT. Patients in the control group underwent surgery but did not receive RT/CRT. System therapy (chemotherapy, immunotherapy, target therapy, etc.) was not taken into account. 3) Study type: cohort. 4) Language: English or Chinese.

The exclusion criteria were as follows: 1) patients were treated with other forms of local treatment, including, but not limited to, radiofrequency ablation, cryoablation, high-intensity focused ultrasound, and others. 2) Duplicate published trials. 3) Studies without enough data.

2.3 Data extraction and quality assessment

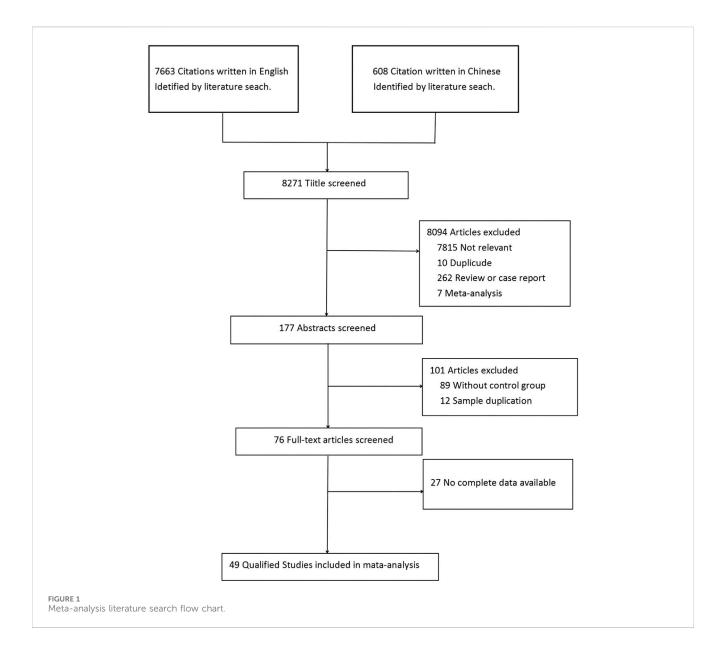
Two authors independently retrieved and assessed the eligible articles. If there was any disagreement, the authors discussed and resolved the issue, with a third author adjudicating if the dispute could not be resolved. The following information was extracted: OS, cancer-specific survival, LR, local recurrence-free survival, diseasefree survival (DFS), distant metastases-free survival (DMFS), and anal sphincter preservation rate. Some data, such as the OS curve, were extracted from images using the Engauge Digitizer software. The data were then independently cross-checked.

Risk of bias was assessed for the included cohort trials using the Cochrane Handbook 5.1.0. and Review Manager 5.3 (3, 13). Funnel plots were used to assess publication bias in the included studies.

2.4 Statistical analysis

Statistical analysis was performed using RevMan (Review Manager, version 5.3 for Windows). Statistical pooling of effect measures was based on the level of heterogeneity among studies, which was assessed using the Cochrane Q test and the I² statistic. No significant heterogeneity was indicated by a P value >0.1 in the Cochrane Q test and an I² statistic less than 50%. The prognostic effect was quantified using the hazard ratio (HR) and odds ratio (OR, with a 95% confidence interval (CI). The HR was calculated using the fixed-effects model with the inverse variance method. The

Abbreviations: (TME), total mesorectal excision; (non-TME-only), other types of surgery; (OS), overall survival; (LCCRT), long-course concurrent chemoradiotherapy; (RT), radiotherapy; (MDT), multidisciplinary treatment; (LARC), locally advanced rectal cancer; (LR), local recurrence; (CRT), concurrent chemoradiotherapy; (DFS), disease-free survival; (DMFS), distant metastases-free survival; (HR), hazard ratio; (OR), odds ratio; (3D-CRT), 3-dimensional conformal radiotherapy; (IMRT), intensity-modulated radiotherapy; (pCR), pathological complete response; (TNT), total neoadjuvant therapy.



OR was calculated using the Mantel-Haenszel method under the fixed-effects model. Publication bias was evaluated by visual inspection of funnel plots. A P value ≤ 0.05 was considered significant (3, 13).

3 Results

3.1 Characteristics of included studies

As shown in Figure 1, a total of 8,271 studies were identified initially using the above search strategy. After reviewing the titles and abstracts, 8,195 studies were excluded. After a thorough review of the full texts, 27 studies were excluded. Finally, 49 studies were eligible for meta-analysis (4, 5, 6, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, and 57), including 26 retrospective studies (6, 21, 27, 28, 29, 30, 31, 32, 33, 34,

35, 36, 38, 39, 40, 41, 43, 45, 46, 48, 49, 51, 53, 55, 56, and 57) and 23 prospective studies (4, 5, 11, 12, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 37, 42, 44, 47, 50, 52, and 54), with a total of 25,679 patients—13,278 in the RT group and 12,401 in the non-RT group (Figure 1). Table 1 lists the identified studies and their main characteristics.

In all included studies, their baselines were comparable. The risk of bias assessment is shown in the supplementary material (Supplementary Figure 1, 2). None of the studies were at high risk of bias.

3.1.1 RT improves sphincter preservation and reduces LR

RT, as a local treatment to surgical resection, has been used in select cases to avoid permanent colostomy and reduce LR (45). Only four studies provided enough data to analyze the OR for sphincter preservation rate (28, 32, 45, 55). A total of 2,405 subjects were included, with 1,510 in the RT group and 895 in the non-RT

TABLE 1 Characteristics of included studies.

Research type	Reference	Median follow-up time (months)	RT technique	Radiotherapy dose (Gy) Gy/day; total dose (Gy)	Group	Number of patients	T/N Stage	Median survival time (months)
Retro	(35)	156	NA	5 25	RT + Surgery	454	T1-T3	NA
					Surgery	454	T1-T3	NA
Retro	(41)	68 64	Linac	1.8 45	TME + CRT	309	T2/T3 N0-N2	NA
					TME + LPLD	176	T2/T3 N0-N2	NA
Retro	(28)	47.4	Linac	NA	CRT	48	T2-T4 N0-N2	NA
				40-45	СТ	60	T2-T4 N0-N2	NA
Retro	(30)	24	NA	1.8-2.0	RTx	28	T1-T4 N0-N2	50
				44-50.4	Non-RTx	40	T1-T4 N0-N2	49
Retro	(55)	36	Linac	1.8	CCRT	37	T3-T4 N0-N2	NA
				50.4	Surgery	86	T3-T4 N0-N2	NA
Retro	(27)	NA	Linac	1.8-2.0/1.8-2.3	nRTx	28	T1-T4	42
				27-30/44.6-52	No-nRTx	65	T1-T4	38
Retro	(43)	29/27	NA	1.8–2.0 45–50.4	RTX	40	T1-T4 N0-N2	27 ± 4.81
					NRTX	46	T1-T4 N0-N2	24 ± 6.76
Retro	(39)	NA	NA	NA	CRT	3022	T1-T3	NA
					None	1,354	T1-T3	NA
Retro	(34)	45.7 ± 19.8	NA	NA 45–50	PCRT + surgery	70	NA N0-N2	NA
					Surgery	70	NA N0-N2	NA
Retro	(36)	43	NA	NA	RT	47	T3-T4 N0-N2	NA
				30-55.8/20-25/10-12.5	No-RT	46	T3-T4 N0-N2	NA
Retro	(40)	58	NA	NA 50.4	CRG	253	T2-T3	NA
				50.4	CG	460	T2-T3	NA
Retro	(53)	71	NA	NA 50	CCRT + TME	90	T3-T4 N0-N2	NA
					TME	94	T3-T4 N0-N2	NA
Retro	(38)	55.8	NA	NA	S + RT	386	T1-T4	NA
					S	635	T1-T4	NA
Retro	(49)	56.4	3DCRT	2	CRT	115	Т3	NA
		57.1		46-55	СТ	150	Т3	NA
Retro	(21)	52	NA	5 25	RT + Surgery	94	T3 N1-N2	NA
					Surgery	57	T3 N1-N2	NA
Retro	(56)	48.1	NA	NA 25 50 4	CRT	102	T2-T3 N0-N2	NA
				25-50.4	СТ	161	T2-T3 N0-N2	NA

(Continued on following page)

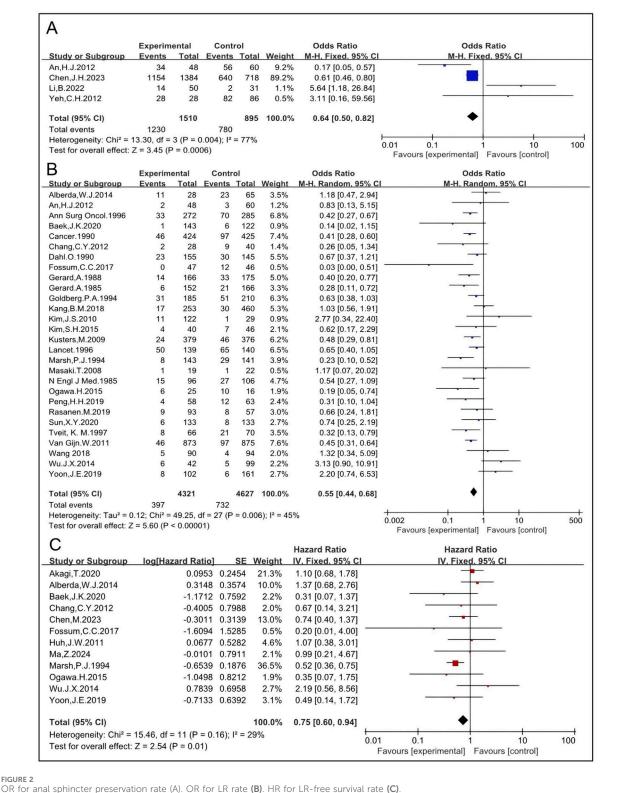
TABLE 1 (Continued) Characteristics of included studies.

Research type	Reference	Median follow-up time (months)	RT technique	Radiotherapy dose (Gy) Gy/day; total dose (Gy)	Group	Number of patients	T/N Stage	Median survival time (months)
Retro	(6)	41.5	NA	1.8-2.0	CRT	189	T2-T3 N1-N3	NA
		43.1		40-50.4	Surgery	649	T2-T3 N1-N3	NA
Retro	(29)	71	NA	1.8-2.0	CCRT	143	Т3	NA
				43.2-60	Surgery	122	Т3	NA
Retro	(48)	65.7 ± 29	NA	1.8-2.0	PCRT	1,258	T1-T3 N0-N2	NA
				45-50.4	Non- PCRT	957	T1-T3 N0-N2	NA
Retro	(51)	45	3DCRT	1.8-2.0	NACRT	185	T2-T3	NA
				45-50.4	Non- NACRT	173	T2-T3	NA
Retro	(46)	26	NA	2	NRCT	55	T3-T4 N0-N2	NA
				50	NCT	22	T3-T4 N0-N2	NA
Retro	(45)	46	NA	1.8-2.0	CRT	50	T2-T3 N0-N+	NA
				46-50.4	СТ	31	T2-T3 N0-N+	NA
Retro	(54)	47.5	NA	40-50	NCRT	76	T3-T4 N0-N+	NA
					NCT	52	T3-T4 N0-N+	NA
Retro	(32)	60	NA	NA	CRT	1,384	T1-T3	NA
					СТ	718	T1-T3	NA
Retro	(33)	33.9	NA	NA	NCRT	80	T2-T3 N0-N2	NA
					NCT	238	T2-T3 N0-N2	NA
Retro	(31)	NA	NA	NA	EP + CCRT	107	T1 N0-N3	NA
					EP	718	T1 N0-N3	NA
Retro	(57)	NA	IMRT/VMRT	NA	RT	69	T2/T3 N0-N2	NA
				45-66.4	Non-RT	294	T2/T3 N0-N2	NA
RCT	(24)	NA	NA	NA 20	Multiple fractions	272	NA	NA
					No-xRT	275	NA	NA
RCT	(16)	NA	Linac	2.3 34.5	RT + Surgery	152	T2-T4	NA
					Surgery	166	T2-T4	NA
RCT	(25)	80	NA	NA	CCRT	46	NA	NA
				40-44	Control	58	NA	NA
RCT	(37)	75	Linac	2.3	RT	166	T2-T4	NA
				34.5	Non-RT	175	T2-T4	NA
RCT	(4)	53	Linac	5	RT	424	T1-T3	NA
				25	Non-RT	425	T1-T3	NA
RCT	(15)	54	Linac	1.75	RT	159	NA	NA
				31.5	Non-RT	150	NA	NA

(Continued on following page)

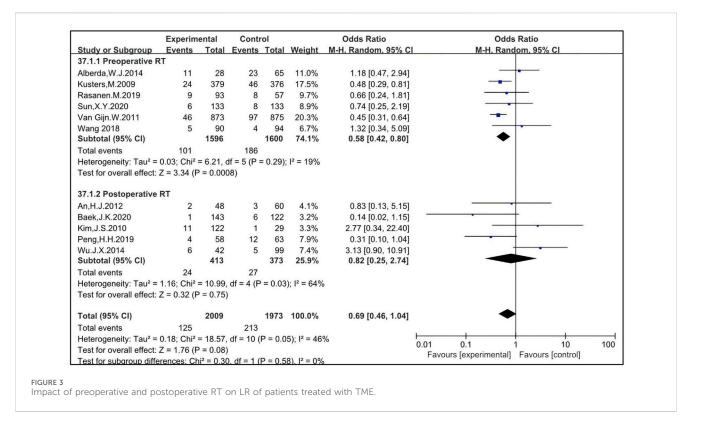
TABLE 1 (Continued) Characteristics of included studies.

Research type	Reference	Median follow-up time (months)	RT technique	Radiotherapy dose (Gy) Gy/day; total dose (Gy)	Group	Number of patients	T/N Stage	Median survival time (months)
RCT	(17)	NA	NA	5 45-60	RT + surgery	228	Dukes A-C2	NA
					Surgery	239	Dukes A-C2	NA
RCT	(47)	NA	Linac	5	RT	143	NA	NA
				20	Non-RT	141	NA	NA
RCT	(26)	50	Linac	5	RT	272	NA	NA
				25	Non-RT	285	NA	NA
RCT	(5)	120	Linac	2.0	RT	139	NA	31
				40	Non-RT	140	NA	24
RCT	(22)	NA	Three-field	2.0	RT	66	Dukes B andC	NA
			technique	46	Non-RT	70	Dukes B and C	NA
RCT	(20)	63	Box of three- field	1.8 38	RT + IORT	69	T1-T3	NA
					TME	44	T1-T3	NA
RCT	(18)	34	NA	18-20	IORT	19	T1-T3	NA
					Control	22	T1-T3	NA
RCT	(44)	84	NA	5	RT	379	T1-T4 N0-N2	NA
				25	Non-RT	376	T1-T4 N0-N2	NA
RCT	(42)	78	Linac	1.8	CRT	122	NA	NA
				50.4-54	СТ	29	NA	NA
RCT	(12)	52	NA	1.8	CRT	64	T3 N1-N2	NA
				45-50.4	СТ	190	T3 N1-N2	NA
RCT	(11)	144	NA	5 25	RT + TME	897	Т0-Т4	139.2
					TME	908	Т0-Т4	139.2
RCT	(50)	30	3D-EBRT	1.8-2.0	RT	206	Т3-Т4	NA
				44-45	Non-RT	178	T3-T4	NA
RCT	(23)	44	3DCRT	2	CRT	42	T3	NA
				50	СТ	99	Т3	NA
RCT	(19)	36	3DCRT	2	preCRT	25	T1-T4 N0-N2	NA
				50	Non- preCRT	16	T1-T4 N0-N2	NA
RCT	(52)	55	NA	1.8	nCRT	395	T3-T4 N0-N+	NA
				50.4	Surgery	395	T3-T4 N0-N+	NA
RCT	(14)	NA	NA	1.8-2.0	RT	174	T2-T3 N0-N2	NA
				50.4-54	Non-RT	92	T2-T3 N0-N2	NA



group. The pooled OR was 0.64 [95% confidence interval (CI): 0.50-0.82, P = 0.0006] (Figure 2), indicating that RT significantly increases the sphincter preservation rate.

A total of 28 studies, including 4,321 patients in the RT group and 4,627 in the non-RT group, were eligible to analyze the LR rate (4, 5, 11, 15, 16, 17, 18, 19, 21, 22, 23, 25, 26, 27, 28, 29, 30, 36, 37, 40, 42, 43, 44, 47, 49, 51, 53, and 56). The pooled OR was 0.55 [95% CI: 0.44-0.68, P < 0.00001] (Figure 2), indicating that the LR rate in the RT group is significantly lower than that in the non-RT group. Twelve studies reported LR-free survival rate, involving



3,205 subjects—1,116 in the RT group and 2,089 in the non-RT group (6, 12, 19, 23, 27, 29, 30, 33, 36, 47, 56, 57). The pooled OR was 0.75 [95% CI: 0.60–0.94, P = 0.01] (Figure 2), indicating that the LR-free survival rate in the RT group is significantly higher than that in the non-RT group. The I² was 45% and RT modalities may be involved in the level of heterogeneity, which has been analyzed below. Therefore, the results should be interpreted with caution.

3.1.2 Preoperative RT improves LR of patients treated with TME while postoperative RT may not

TME is one of the first-choice surgical treatments for middle and low LARC because it significantly reduces LR, thus questioning the necessity of RT. To address this question, the impact of RT before and after TME on LR was analyzed.

Six studies were eligible to analyze the impact of preoperative RT, with 1,596 patients enrolled in the RT group and 1,600 in the non-RT group (11, 21, 27, 44, 51, 53). The OR was 0.58 [95% CI: 0.42–0.80, P = 0.0008]. Five studies were eligible to analyze the impact of postoperative RT, with 413 patients enrolled in the RT group and 373 in the non-RT group (23, 28, 29, 42, 49). The OR was 0.82 [95% CI: 0.25–2.74, P = 0.75]. The pooled OR for LR with the combination of preoperative and postoperative RT was 0.69 [95% CI: 0.46–1.04, P = 0.08] (Figure 3). This indicates that preoperative RT improves LR in patients treated with TME while postoperative RT may not.

3.1.3 Preoperative RT improves LR of patients treated with non-TME-only surgery

Sixteen studies included patients who underwent surgical procedures other than TME or not clearly defined as "radical surgery". These studies were eligible to analyze the impact of preoperative and postoperative RT on LR in patients treated with non-TME surgeries. Eleven studies were eligible to analyze the impact of preoperative RT, with 1,748 patients enrolled in the RT group and 1,795 in the non-RT group (4, 5, 15, 16, 17, 19, 26, 36, 37, 43, 47). The OR was 0.45 [95% CI: 0.35–0.57, P < 0.00001]. Five studies were eligible to analyze the impact of postoperative RT, with 545 patients enrolled in the RT group and 837 in the non-RT group (22, 25, 30, 40, 56). The OR was 0.68 [95% CI: 0.35–1.31, P = 0.25]. The pooled OR for LR with the combination of preoperative and postoperative RT was 0.49 [95% CI: 0.38–0.64, P < 0.00001] (Figure 4). Preoperative RT improves the LR of patients treated with non-TME-only surgery.

3.1.4 RT improves survival

Thirty-nine studies, including 18 retrospective and 19 prospective studies, were eligible to analyze the impact of preoperative and postoperative RT on OS in rectal cancer patients. The HRs for OS in the retrospective (6, 27, 28, 29, 30, 31, 33, 35, 36, 41, 43, 45, 46, 49, 51, 53, 55, 57) and the prospective (4, 5, 12, 14, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26, 37, 42, 47, 52, 54) studies were 0.87 [95% CI: 0.78-0.97, P = 0.01] and 0.87 [95% CI: 0.81-0.94, P = 0.0002], respectively. The pooled HR of both retrospective and prospective studies was 0.87 [95%CI: 0.82-0.93, p = 0.0002] (Figure 5), indicating that RT significantly improves OS. Three studies reported cancer-specific survival (32, 44, 50). The pooled HR was 0.78 [95%CI: 0.68-0.90, P = 0.0005] (Supplementary Figure S3), indicating that RT improves cancer-specific survival. The HRs for OS and cancer-specific survival concordantly support that RT improves survival. The DFS was analyzed and 21 studies were eligible (12, 14, 18, 20, 25, 27, 28, 29, 30, 33, 34, 41, 45, 46, 48, 49, 51, 53, 54, 55, 56). The pooled HR, including 3,037 patients in the RT

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H, Random, 95% Cl
38.1.1 Preoperative R1	-						
Ann Surg Oncol.1996	33	272	70	285	10.1%	0.42 [0.27, 0.67]	
Cancer.1990	46	424	97	425	11.1%	0.41 [0.28, 0.60]	
Dahl.O.1990	23	155	30	145	8.2%	0.67 [0.37, 1.21]	
Fossum, C.C.2017	0	47	12	46	0.8%	0.03 [0.00, 0.51]	<u>← · · · · · · · · · · · · · · · · · · ·</u>
Gerard, A.1988	14	166	33	175	7.4%	0.40 [0.20, 0.77]	
Gerard.A.1985	6	152	21	166	5.0%	0.28 [0.11, 0.72]	
Goldberg.P.A.1994	31	185	51	210	9.5%	0.63 [0.38, 1.03]	
Kim,S.H.2015	4	40	7	46	3.1%	0.62 [0.17, 2.29]	
_ancet.1996	50	139	65	140	9.7%	0.65 [0.40, 1.05]	
Marsh, P.J. 1994	8	143	29	141	5.9%	0.23 [0.10, 0.52]	
Ogawa.H.2015	6	25	10	16	2.9%	0.19 [0.05, 0.74]	
Subtotal (95% CI)		1748		1795	73.5%	0.45 [0.35, 0.57]	•
Total events	221		425				
38.1.2 Postoperative R							
Chang,C.Y.2012	2	28	9	40	2.2%	0.26 [0.05, 1.34]	
Kang,B.M.2018	17	253	30		8.0%	1.03 [0.56, 1.91]	
N Engl J Med.1985	15	96	27	106	7.0%	0.54 [0.27, 1.09]	
Tveit, K. M.1997	8	66	21	70	5.3%	0.32 [0.13, 0.79]	
Yoon,J.E.2019 Subtotal (95% Cl)	8	102 545	6	161 837	4.0% 26.5%	2.20 [0.74, 6.53] 0.68 [0.35, 1.31]	-
Total events	50		93				
Heterogeneity: Tau ² = 0	.33; Chi ² =	10.54,	df = 4 (P =	= 0.03)	l² = 62%		
Test for overall effect: Z	= 1.16 (P	= 0.25)					
Total (95% CI)		2293		2632	100.0%	0.49 [0.38, 0.64]	◆
Total events	271		518				T
Heterogeneity: Tau ² = 0				9 = 0.01); I ² = 49%)	0.01 0.1 1 10 100
	= 5.40 (P)	< 0.000	01)				Favours [experimental] Favours [control]
Test for overall effect: Z Test for subgroup difference		2 = 1 38	df = 1/D	= 0.24	$ 1^2 = 27 A$	0/2	Tavours [experimental] Tavours [control]

Impact of preoperative and postoperative RT on LR of patients treated with non-TME.

group and 2,903 in the non-RT group, was 0.95 [95% CI: 0.86–1.06, P = 0.35] (Figure 5), indicating that there is no significant difference in DFS between the RT group and the non-RT group. The metastasis-free survival was also analyzed and six studies were eligible (19, 27, 33, 36, 47, 57). The pooled HR, including 489 patients in the RT group and 887 in the non-RT group, was 1.02 [95% CI: 0.84–1.24, P = 0.86] (Supplementary Figure S4), indicating there is no significant difference in metastasis-free survival between the RT group and the non-RT group. Taken together, these results imply that RT may not improve DFS or metastasis-free survival.

CRT yields better results than RT alone in terms of survival outcomes in certain cancer types. The impact of CRT on OS was analyzed. Thirtyeight studies, of which 26 studies (6, 12, 14, 19, 22, 23, 25, 27, 28, 29, 30, 31, 33, 36, 41, 42, 43, 45, 46, 49, 50, 51, 52, 53, 54, 55) employed CRT and 11 (4, 5, 15, 16, 17, 18, 24, 26, 35, 37, 47) employed RT-alone, were eligible. The HRs of CRT and RT alone were 0.91 [95% CI: 0.82–1.02, p = 0.10] and 0.85 [95% CI: 0.80–0.92, P < 0.00001]. The pooled HR, including 2,867 patients in the RT group and 3,895 in the non-RT group, was 0.87 [95% CI: 0.82–0.92, P < 0.00001] (Supplementary Figure S5). Further analysis was conducted understand these results.

3.1.5 Preoperative RT improves OS while postoperative RT might not

Although there has been a paradigm shift from a postoperative to a preoperative approach, few randomized studies have directly compared preoperative RT with postoperative RT (58, 59). Here, the effects of preoperative and postoperative RT on OS were analyzed. The pooled HR of preoperative RT of 27 studies, including 5,152 patients in the RT group and 5,835 in the non-RT group, was 0.89 [95% CI: 0.85–0.95, P < 0.0001] (4, 5, 6, 11, 14, 15, 16, 17, 19, 24, 26, 27, 33, 35, 36, 37, 43, 45, 46, 47, 50, 51, 52, 53, 54, 55, 57) (Figure 6). The pooled HR of postoperative RT of 10 studies, including 781 patients in the RT group and 1,536 in the non-RT group, was 1.05 [95% CI: 0.89–1.23, P = 0.60] (12, 22, 23, 25, 28, 29, 30, 31, 42, 49) (Figure 6), indicating that preoperative RT significantly improves OS while postoperative RT might not.

The effects of CRT before and after surgery on OS were analyzed. The pooled HR of preoperative CRT of 15 studies, including 1,777 patients in the RT group and 2,183 in the non-RT group, was 0.85 [95% CI: 0.72–1.00, P = 0.05] (6, 14, 19, 27, 33, 36, 43, 45, 46, 50, 51, 52, 53, 54, 55) (Figure 7). The pooled HR of postoperative CRT of 10 studies, including 781 patients in the RT group and 1,536 in the non-RT group, was 1.05 [95% CI: 0.89–1.23, P = 0.60] (12, 22, 23, 25, 28, 29, 30, 31, 42, 49) (Figure 7), indicating that preoperative CRT significantly improves OS while postoperative CRT might not. These results are concordant with those of RT and indicate that preoperative RT/CRT significantly improves OS while postoperative RT/CRT might not.

The impact of different RT regimens on OS was analyzed. LCRT typically involves a total dose of approximately 45–50 Gy delivered in 1.8–2 Gy fractions over a period of 5–6 weeks, whereas SCRT consists of a total dose of approximately 25 Gy delivered in 5 Gy fractions over the

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed, 95% CI	Hazard Ratio IV. Fixed, 95% Cl
1.1.1 retrospective Akagi,T.2020	-0.0513	0.2882	1.1%	0.95 [0.54, 1.67]	
Alberda, W.J.2014		0.3622		1.20 [0.59, 2.44]	
An,H.J.2012		0.2644		1.36 [0.81, 2.28]	
Baek, J.K.2020		0.7494		1.39 [0.32, 6.04]	
Chang,C.Y.2012		0.4104		0.76 [0.34, 1.70]	
Chen,H.2024 Chen,M.2023		0.1527	3.9% 0.6%	1.16 [0.86, 1.56] 0.85 [0.40, 1.81]	
olkesson,J.2005		0.0818		0.81 [0.69, 0.95]	-
ossum,C.C.2017		0.3475	0.8%	0.83 [0.42, 1.64]	
Kim, J.C.2007	-0.5108	0.17	3.2%	0.60 [0.43, 0.84]	
Kim,S.H.2015 .i,B.2022		0.3251 0.5342	0.9% 0.3%	0.87 [0.46, 1.65]	
i.w.c.2021		1.2461	0.3%	1.51 [0.53, 4.30] 0.23 [0.02, 2.64]	
Aa,Z.2024		0.3474		0.81 [0.41, 1.60]	
Peng,H.H.2019		0.3603	0.7%	0.77 [0.38, 1.56]	
Sun,X.Y.2020		0.2154	2.0%	0.90 [0.59, 1.37]	
Vang 2018 (eh,C.H.2012	-0.0408	0.398	0.6% 0.1%	0.96 [0.44, 2.09] 2.04 [0.44, 9.46]	
Subtotal (95% CI)	0.7 120	0.7020	31.2%	0.87 [0.78, 0.97]	•
Heterogeneity: Chi ² = 1 Test for overall effect: 2		(6); $I^2 = 0$	1%		
1.1.2 prospective Ann Surg Oncol.1996	-0 1995	0.1185	6.5%	0.82 [0.65, 1.03]	-
Br J Surg.1984		0.1168		0.88 [0.70, 1.11]	-
Cai.J.2024	0.3148	0.5246	0.3%	1.37 [0.49, 3.83]	
Cancer.1990		0.0963		0.93 [0.77, 1.12]	-
Dahl.O.1990 Gerard,A.1988		0.2306	1.7% 3.7%	0.99 [0.63, 1.56] 0.79 [0.58, 1.08]	I
Gerard, A. 1988 Gerard, A. 1985		0.1577		0.80 [0.55, 1.16]	
Goldberg.P.A.1994	0.0488	0.1078	7.8%	1.05 [0.85, 1.30]	+ 1
Huh,J.W.2011	0.077	0.166		1.08 [0.78, 1.50]	
(im,J.S.2010	0.0198	0.76		1.02 [0.23, 4.52]	
.ancet.1996 Marsh,P.J.1994		0.1169	6.7% 12.6%	0.83 [0.66, 1.04] 0.78 [0.66, 0.92]	-
Aasaki.T.2008		0.6143	0.2%	0.50 [0.15, 1.67]	
V Engl J Med.1985		0.3084	1.0%	0.97 [0.53, 1.78]	
Dgawa.H.2015		0.4348		0.68 [0.29, 1.59]	
Sun,Y.2017 Tveit, K. M.1997		0.1691 0.2898	3.2% 1.1%	0.78 [0.56, 1.09] 0.60 [0.34, 1.06]	
Vu.J.X.2014		0.4074		1.40 [0.63, 3.11]	
(an,H.2022		0.405	0.6%	1.15 [0.52, 2.54]	
Subtotal (95% CI) Heterogeneity: Chi ² = 1 Fest for overall effect: 2			68.8%	0.87 [0.81, 0.94]	•
	2 = 3.74 (F = 0.0002)		100.00/		
Fotal (95% CI) Heterogeneity: Chi² = 3	1 00 df = 36 (D = 0.7	(0): 12 = 0	100.0%	0.87 [0.82, 0.93]	
					0.02 0.1 1 10 50 Favours [experimental] Favours [control]
est for overall effect:	L = 4.55 (F < 0.00001)	f = 1 (P = 1)	= 0.98), l ² =	= 0%	ravours [experimental] - ravours [control]
est for subgroup diffe				Use and Datis	Userend Datis
Fest for subgroup diffe	rences: Chi² = 0.00, d		Weight	Hazard Ratio	Hazard Ratio
Fest for subgroup diffe B Study or Subgroup	rences: Chi ² = 0.00. d log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	Hazard Ratio IV. Fixed. 95% Cl
Fest for subgroup diffe B Study or Subgroup Alberda,W.J.2014	rences: Chi ² = 0.00, d log[Hazard Ratio] 0	SE 0.2958	3.1%	IV, Fixed, 95% CI 1.00 [0.56, 1.79]	The second se
Fest for subgroup diffe Study or Subgroup Alberda,W.J.2014 An,H.J.2012	rences: Chi ² = 0.00, d <u>log[Hazard Ratio]</u> 0 0.2469	SE 0.2958 0.1854	3.1% 8.0%	IV, Fixed, 95% CI 1.00 [0.56, 1.79] 1.28 [0.89, 1.84]	The second se
Fest for subgroup diffe Study or Subgroup Alberda,W.J.2014 An,H.J.2012	rences: Chi ² = 0.00, d [log[Hazard Ratio] 0 0.2469 -0.4005	SE 0.2958 0.1854 0.41	3.1%	IV, Fixed, 95% CI 1.00 [0.56, 1.79]	The second se
Fest for subgroup diffe Study or Subgroup Alberda,W.J.2014 An,H.J.2012 Baek,J.K.2020	rences: Chi ² = 0.00, d <u>log[Hazard Ratio]</u> 0 0.2469	SE 0.2958 0.1854 0.41	3.1% 8.0%	IV, Fixed, 95% CI 1.00 [0.56, 1.79] 1.28 [0.89, 1.84]	The second se
Fest for subgroup diffe Study or Subgroup Nerda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Cai. J. 2024	rences: Chi ² = 0.00, d [log[Hazard Ratio] 0 0.2469 -0.4005	SE 0.2958 0.1854 0.41 0.3028	3.1% 8.0% 1.6%	IV. Fixed. 95% CI 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda,W.J.2014 An,H.J.2012 Baek,J.K.2020 Cai.J.2024 Chang,C.Y.2012	rences: Chi ² = 0.00. d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054	SE 0.2958 0.1854 0.41 0.3028 0.2898	3.1% 8.0% 1.6% 3.0% 3.3%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59]	The second se
Test for subgroup diffe Study or Subgroup Niberda,W.J.2014 An,H.J.2012 Saek,J.K.2020 Cai.J.2024 Chang,C.Y.2012 Chen,M.2023	rences: Chi ² = 0.00. d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.2898 0.1936	3.1% 8.0% 1.6% 3.0% 3.3% 7.3%	IV. Fixed, 95% CI 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11]	The second se
Fest for subgroup diffe Study or Subgroup Alberda, W.J.2014 An, H.J.2012 Saek, J.K.2020 Cai.J.2024 Chang, C.Y.2012 Chen, M.2023 Cho, S.H.2017	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53]	The second se
est for subgroup diffe Study or Subgroup Nberda, W.J.2014 An,H.J.2012 Saek, J.K.2020 Cai.J.2024 Chang, C.Y.2012 Chen,M.2023 Cho,S.H.2017 Huh,J.W.2011	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311	SE 0.2958 0.1854 0.3028 0.3028 0.2898 0.1936 0.4292 0.1949	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85]	The second se
Test for subgroup diffe	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.1949 0.2029	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95]	The second se
Fest for subgroup diffe Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 2ai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.1949 0.2029	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 .i, B. 2022	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.1949 0.2029 0.5413	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 i, B. 2022 i, w. c. 2021	rences: Chi ² = 0.00. d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.1949 0.2029 0.5413 1.0859	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.9% 0.2%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.05, 3.53]	The second se
est for subgroup diffe Study or Subgroup Nberda, W.J.2014 An, H.J.2012 Staak, J.K.2020 Cai.J.2024 Chang, C.Y.2012 Chen, M.2023 Cho, S.H.2017 tuh, J.W.2011 Kim, J.C.2007 i, B.2022 Jasaki, T.2008	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.1949 0.2029 0.5413 1.0859 0.702	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.9% 0.2% 0.6%	IV. Fixed. 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.05, 3.53] 0.95 [0.24, 3.76]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda,W.J.2014 An,H.J.2012 3aek,J.K.2020 Cai.J.2024 Chang,C.Y.2012 Chen,M.2023 Cho,S.H.2017 Huh,J.W.2011 Kim,J.C.2007 Li,B.2022 Li,w.c.2021 Masaki.T.2008 N Engl J Med.1985	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863	SE 0.2958 0.1854 0.3028 0.2898 0.4292 0.4292 0.2029 0.2029 0.2029 0.5413 1.0859 0.702 0.3011	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.9% 0.2% 0.6% 3.0%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2021 Masaki, T. 2008 N Engl J Med. 1985 Ch, S. G. 2020	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296	SE 0.2958 0.1854 0.3028 0.2898 0.1936 0.4292 0.5413 1.0859 0.702 0.3011 0.0861	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W.J.2014 An, H.J.2012 Baek, J.K.2020 Cai, J.2024 Chang, C.Y.2012 Chen, M.2023 Cho, S.H.2017 Huh, J.W.2011 Kim, J.C.2007 i, J.B.2022 J, w.c.2021 Masaki, T.2008 N Engl J Med. 1985 Dh, S.G.2020 Pacelli, F.2004	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296 -0.2357	SE 0.2958 0.1854 0.3028 0.2898 0.1936 0.2898 0.1936 0.2029 0.5413 1.0859 0.702 0.3011 0.0861 0.387	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.9% 0.2% 0.6% 3.0% 36.9% 1.8%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W.J.2014 An, H.J.2012 Baek, J.K.2020 Cai, J.2024 Chang, C.Y.2012 Chen, M.2023 Cho, S.H.2017 Huh, J.W.2011 Kim, J.C.2007 i, J.B.2022 J, w.c.2021 Masaki, T.2008 N Engl J Med. 1985 Dh, S.G.2020 Pacelli, F.2004	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296 -0.2357	SE 0.2958 0.1854 0.3028 0.2898 0.1936 0.4292 0.5413 1.0859 0.702 0.3011 0.0861	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Cai. J. 2024 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 i, B. 2022 J, w. c. 2021 Masaki, T. 2008 N Engl J Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Peng, H. H. 2019	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296 -0.2357	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4929 0.1949 0.2029 0.5413 1.0859 0.702 0.3011 0.0861 0.387 0.3218	3.1% 8.0% 1.6% 3.0% 3.3% 7.3% 1.5% 7.2% 6.6% 0.9% 0.2% 0.6% 3.0% 36.9% 1.8%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69]	The second se
Fest for subgroup diffe Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Saek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2011 Kim, J. C. 2007 J. W. C. 2021 Masaki, T. 2008 N Engl. J. Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Pacelli, F. 2004 Pang, H. H. 2019 Sun, X. Y. 2020	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296 -0.2357 -0.478 -0.3011	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.2029 0.5413 1.0859 0.702 0.3011 0.3861 0.3218 0.3218	3.1% 8.0% 1.6% 3.3% 7.3% 1.5% 7.2% 6.6% 0.9% 0.2% 0.6% 3.0% 3.0% 3.0% 3.0% 3.6,9% 1.8% 2.6% 5.6%	$\begin{array}{c} \textbf{IV, Fixed, 95\% Cl} \\ 1.00 [0.56, 1.79] \\ 1.28 [0.89, 1.84] \\ 0.67 [0.30, 1.50] \\ 1.05 [0.58, 1.90] \\ 0.90 [0.51, 1.59] \\ 0.76 [0.52, 1.11] \\ 1.09 [0.47, 2.53] \\ 1.26 [0.86, 1.85] \\ 0.64 [0.43, 0.95] \\ 1.04 [0.36, 3.00] \\ 0.42 [0.05, 3.53] \\ 0.95 [0.24, 3.76] \\ 0.83 [0.46, 1.50] \\ 1.03 [0.87, 1.22] \\ 0.79 [0.37, 1.69] \\ 0.62 [0.33, 1.16] \\ 0.74 [0.48, 1.14] \end{array}$	The second se
Fest for subgroup diffe Budy or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Saek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2021 Masaki. T. 2008 N Engl J Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Peng, H. H. 2019 Sun, X.Y. 2020 Wang 2018	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296 -0.2357 -0.478 -0.3011 0	SE 0.2958 0.1854 0.411 0.3028 0.2898 0.1936 0.4292 0.2029 0.5413 1.0859 0.702 0.3011 0.0861 0.3218 0.3218 0.2209 0.3962	3.1% 8.0% 1.6% 3.3% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7%	IV. Fixed. 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.5, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69] 0.62 [0.33, 1.16] 0.74 [0.48, 1.14] 1.00 [0.46, 2.17]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 3aek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2011 Kim, J. C. 2007 Pacelli, F. 2004 Peng, H. H. 2019 Sun, X. Y. 2020 Wang 2018 Yan, H. 2022	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.6513 -0.1863 0.0296 -0.2357 -0.478 -0.3011 0 -0.3011 -0.3012 -0.3011 -0.3011 -0.3012 -0.3012 -0.3011 -0.3012 -0.3011 -0.3012 -0.3011 -0.3012 -0.3	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.4292 0.5413 1.0859 0.702 0.3011 0.387 0.3218 0.2209 0.3962 0.3953	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.9% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69] 0.67 [0.48, 1.14] 1.00 [0.46, 2.17] 0.94 [0.47, 1.88]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2011 Kim, J. C. 2007 J. B. 2022 Li, W. C. 2021 Masaki, T. 2008 N Engl J. Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Pacelli, F. 2004 Pacelli	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 0.0296 -0.2357 -0.478 -0.3011 0 -0.0619 0.5365	SE 0.2958 0.1854 0.1854 0.2898 0.2898 0.2898 0.2029 0.5413 1.0859 0.702 0.3011 0.3871 0.3871 0.3218 0.3962 0.3537 0.3876	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2% 1.8%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69] 0.62 [0.33, 1.16] 0.74 [0.46, 2.17] 0.94 [0.47, 1.88] 1.71 [0.80, 3.66]	The second se
Fest for subgroup diffect: : Fest for subgroup diffe B Study or Subgroup diffe Alberda,W.J.2014 An,H.J.2012 3aek,J.K.2020 Cai.J.2024 Chang,C.Y.2012 Cha,S.H.2017 Huh,J.W.2011 Kim,J.C.2007 i,B.2022 J,w.c.2021 Masaki.T.2008 N Engl J Med.1985 Dh,S.G.2020 Pacelli,F.2004 Pan,H.H.2019 Sun,X.Y.2020 Wang 2018 (an,H.2022 (eh,C.H.2012 (oon,J.E.2019	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.6513 -0.1863 0.0296 -0.2357 -0.478 -0.3011 0 -0.3011 -0.3012 -0.3011 -0.3011 -0.3012 -0.3012 -0.3011 -0.3012 -0.3011 -0.3012 -0.3011 -0.3012 -0.3	SE 0.2958 0.1854 0.1854 0.2898 0.2898 0.2898 0.2029 0.5413 1.0859 0.702 0.3011 0.3871 0.3871 0.3218 0.3962 0.3537 0.3876	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.9% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69] 0.67 [0.48, 1.14] 1.00 [0.46, 2.17] 0.94 [0.47, 1.88]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Baek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2011 Kim, J. C. 2007 J. B. 2022 Li, W. C. 2021 Masaki, T. 2008 N Engl J. Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Pacelli, F. 2004 Pacelli	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 0.0296 -0.2357 -0.478 -0.3011 0 -0.0619 0.5365	SE 0.2958 0.1854 0.1854 0.2898 0.2898 0.2898 0.2029 0.5413 1.0859 0.702 0.3011 0.3871 0.3871 0.3218 0.3962 0.3537 0.3876	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2% 1.8%	IV. Fixed, 95% Cl 1.00 [0.56, 1.79] 1.28 [0.89, 1.84] 0.67 [0.30, 1.50] 1.05 [0.58, 1.90] 0.90 [0.51, 1.59] 0.76 [0.52, 1.11] 1.09 [0.47, 2.53] 1.26 [0.86, 1.85] 0.64 [0.43, 0.95] 1.04 [0.36, 3.00] 0.42 [0.05, 3.53] 0.95 [0.24, 3.76] 0.83 [0.46, 1.50] 1.03 [0.87, 1.22] 0.79 [0.37, 1.69] 0.62 [0.33, 1.16] 0.74 [0.46, 2.17] 0.94 [0.47, 1.88] 1.71 [0.80, 3.66]	The second se
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Saek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2021 Masaki. T. 2008 N Engl J Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Pacelli, F. 2019 Kotal (95% CI)	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.8675 -0.0513 -0.1863 0.0296 -0.2357 -0.478 -0.3011 0 -0.4619 0.5365 -0.6162	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.2029 0.5413 1.0859 0.702 0.3011 0.3817 0.3218 0.3218 0.3209 0.3537 0.3876 0.5329	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2% 1.8% 1.0%	$\begin{array}{c} \textbf{IV, Fixed, 95\% Cl} \\ 1.00 [0.56, 1.79] \\ 1.28 [0.89, 1.84] \\ 0.67 [0.30, 1.50] \\ 1.05 [0.58, 1.90] \\ 0.90 [0.51, 1.59] \\ 0.76 [0.52, 1.11] \\ 1.09 [0.47, 2.53] \\ 1.26 [0.86, 1.85] \\ 0.64 [0.43, 0.95] \\ 1.04 [0.36, 3.00] \\ 0.42 [0.05, 3.53] \\ 0.95 [0.24, 3.76] \\ 0.83 [0.46, 1.50] \\ 1.03 [0.87, 1.22] \\ 0.79 [0.37, 1.69] \\ 0.62 [0.33, 1.16] \\ 0.62 [0.33, 1.16] \\ 0.74 [0.48, 1.14] \\ 1.00 [0.46, 2.17] \\ 0.94 [0.47, 1.88] \\ 1.71 [0.80, 3.66] \\ 0.54 [0.19, 1.53] \\ \end{array}$	IV. Fixed. 95% Cl
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Saek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Li, B. 2022 Li, w. c. 2021 Masaki, T. 2008 V Engl J Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Pang, H. H. 2019 Sun, X.Y. 2020 Vang 2018 Yan, H. 2022 Yoh, C. H. 2012 Yoon, J. E. 2019 Total (95% CI) Heterogeneity: Chi ² = 1	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.6175 -0.0513 -0.1863 0.0296 -0.2357 -0.478 -0.3011 0 -0.3615 -0.3615 -0.6162 19.19, df = 20 (P = 0.4)	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.2029 0.5413 1.0859 0.702 0.3011 0.3817 0.3218 0.3218 0.3209 0.3537 0.3876 0.5329	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2% 1.8% 1.0%	$\begin{array}{c} \textbf{IV, Fixed, 95\% Cl} \\ 1.00 [0.56, 1.79] \\ 1.28 [0.89, 1.84] \\ 0.67 [0.30, 1.50] \\ 1.05 [0.58, 1.90] \\ 0.90 [0.51, 1.59] \\ 0.76 [0.52, 1.11] \\ 1.09 [0.47, 2.53] \\ 1.26 [0.86, 1.85] \\ 0.64 [0.43, 0.95] \\ 1.04 [0.36, 3.00] \\ 0.42 [0.05, 3.53] \\ 0.95 [0.24, 3.76] \\ 0.83 [0.46, 1.50] \\ 1.03 [0.87, 1.22] \\ 0.79 [0.37, 1.69] \\ 0.62 [0.33, 1.16] \\ 0.62 [0.33, 1.16] \\ 0.74 [0.48, 1.14] \\ 1.00 [0.46, 2.17] \\ 0.94 [0.47, 1.88] \\ 1.71 [0.80, 3.66] \\ 0.54 [0.19, 1.53] \\ \end{array}$	IV. Fixed. 95% Cl
Fest for subgroup diffe B Study or Subgroup Alberda, W. J. 2014 An, H. J. 2012 Saek, J. K. 2020 Cai. J. 2024 Chang, C. Y. 2012 Chen, M. 2023 Cho, S. H. 2017 Huh, J. W. 2011 Kim, J. C. 2007 Huh, J. W. 2011 Kim, J. C. 2007 J. W. C. 2021 Masaki. T. 2008 N Engl. J. Med. 1985 Dh, S. G. 2020 Pacelli, F. 2004 Pacelli, F. 2004 Pacelli, F. 2004 Pang, H. H. 2019 Sun, X. Y. 2020 Wang 2018 fan, H. 2022 (eh, C. H. 2012 (con, J. E. 2019	rences: Chi ² = 0.00, d log[Hazard Ratio] 0 0.2469 -0.4005 0.0488 -0.1054 -0.2744 0.0862 0.2311 -0.4463 0.0392 -0.6175 -0.0513 -0.1863 0.0296 -0.2357 -0.478 -0.3011 0 -0.3615 -0.3615 -0.6162 19.19, df = 20 (P = 0.4)	SE 0.2958 0.1854 0.41 0.3028 0.2898 0.1936 0.4292 0.2029 0.5413 1.0859 0.702 0.3011 0.3817 0.3218 0.3218 0.3209 0.3537 0.3876 0.5329	3.1% 8.0% 1.6% 3.0% 7.3% 1.5% 7.2% 6.6% 0.2% 0.6% 3.0% 36.9% 1.8% 2.6% 5.6% 1.7% 2.2% 1.8% 1.0%	$\begin{array}{c} \textbf{IV, Fixed, 95\% Cl} \\ 1.00 [0.56, 1.79] \\ 1.28 [0.89, 1.84] \\ 0.67 [0.30, 1.50] \\ 1.05 [0.58, 1.90] \\ 0.90 [0.51, 1.59] \\ 0.76 [0.52, 1.11] \\ 1.09 [0.47, 2.53] \\ 1.26 [0.86, 1.85] \\ 0.64 [0.43, 0.95] \\ 1.04 [0.36, 3.00] \\ 0.42 [0.05, 3.53] \\ 0.95 [0.24, 3.76] \\ 0.83 [0.46, 1.50] \\ 1.03 [0.87, 1.22] \\ 0.79 [0.37, 1.69] \\ 0.62 [0.33, 1.16] \\ 0.62 [0.33, 1.16] \\ 0.74 [0.48, 1.14] \\ 1.00 [0.46, 2.17] \\ 0.94 [0.47, 1.88] \\ 1.71 [0.80, 3.66] \\ 0.54 [0.19, 1.53] \\ \end{array}$	IV. Fixed. 95% Cl

FIGURE 5 Pooled HRs d with RT (A) tients treated with RT (B).

course of 1 week. Sixteen studies, including 2,092 patients in the RT group and 2,560 in the non-RT group, were eligible to analyze the impact of preoperative LCRT. The pooled HR was 0.86 [95% CI: $0.76-0.97, P=0.01]\ (5, 6, 14, 15, 16, 19, 27, 37, 43, 45, 46, 51, 52, 53, 54,$ 57) (Figure 8), indicating that preoperative LCRT significantly improves OS. Nine studies, including 674 patients in the RT group and 818 in the non-RT group, were eligible to analyze the impact of postoperative LCRT. The pooled HR was 1.00 [95% CI: 0.82–1.22, P = 0.98] (12, 22,

A				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV. Fixed. 95% C	IV. Fixed, 95% CI
Akagi,T.2020	-0.0513	0.2882	1.0%	0.95 [0.54, 1.67]	
Alberda, W.J.2014	0.1823	0.3622	0.6%	1.20 [0.59, 2.44]	
Ann Surg Oncol.1996	-0.1985	0.1185	5.7%	0.82 [0.65, 1.03]	-
Br J Surg.1984	-0.1278	0.1168	5.9%	0.88 [0.70, 1.11]	
Cai.J.2024	0.3148	0.5246	0.3%	1.37 [0.49, 3.83]	
Cancer.1990	-0.0726	0.0963	8.7%	0.93 [0.77, 1.12]	-
Chen,M.2023	-0.1625	0.3846	0.5%	0.85 [0.40, 1.81]	
Dahl.O.1990	-0.0101	0.2306	1.5%	0.99 [0.63, 1.56]	
Folkesson, J.2005	-0.2107	0.0818	12.0%	0.81 [0.69, 0.95]	-
Fossum, C.C.2017	-0.1863	0.3475	0.7%	0.83 [0.42, 1.64]	
Gerard, A. 1988	-0.2357	0.1577	3.2%	0.79 [0.58, 1.08]	
Gerard.A.1985	-0.2231	0.1912	2.2%	0.80 [0.55, 1.16]	
Goldberg.P.A.1994	0.0488	0.1078	6.9%	1.05 [0.85, 1.30]	+
Kim,S.H.2015	-0.1393	0.3251	0.8%	0.87 [0.46, 1.65]	
Lancet.1996	-0.1863	0.1169	5.9%	0.83 [0.66, 1.04]	-
Li,B.2022	0.4121	0.5342	0.3%	1.51 [0.53, 4.30]	
Li,w.c.2021	-1.4697	1.2461	0.1%	0.23 [0.02, 2.64]	
Ma,Z.2024	-0.2107	0.3474	0.7%	0.81 [0.41, 1.60]	
Marsh, P.J. 1994	-0.2485	0.0852	11.1%	0.78 [0.66, 0.92]	-
Ogawa.H.2015	-0.3857	0.4348	0.4%	0.68 [0.29, 1.59]	
Spitale, A.2012	-0.5621	0.2205	1.7%	0.57 [0.37, 0.88]	
Sun,X.Y.2020	-0.1054	0.2154	1.7%	0.90 [0.59, 1.37]	
Sun,Y.2017	-0.2485	0.1691	2.8%	0.78 [0.56, 1.09]	-
Van Gijn.W.2011	0.0296	0.0576	24.2%	1.03 [0.92, 1.15]	†
Wang 2018	-0.0408	0.398	0.5%	0.96 [0.44, 2.09]	
Yan,H.2022	0.1398	0.405	0.5%	1.15 [0.52, 2.54]	
Yeh,C.H.2012	0.7129	0.7826	0.1%	2.04 [0.44, 9.46]	
Total (95% CI)			100.0%	0.89 [0.85, 0.95]	•
Heterogeneity: Chi ² = 24		2); $I^2 = 0$	%		0.02 0.1 1 10 50
Test for overall effect: Z	= 3.95 (P < 0.0001)				Favours [experimental] Favours [control]
В				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV. Fixed, 95% CI	IV. Fixed. 95% Cl
An,H.J.2012	0.3075 (10.3%		
	0.3293		1.3%	1.36 [0.81, 2.28]	
Baek,J.K.2020 Chang,C.Y.2012	-0.2744 (4.3%	1.39 [0.32, 6.04] 0.76 [0.34, 1.70]	
0.			4.3%		
Chen,H.2024	0.1484 (1.16 [0.86, 1.56]	
Huh,J.W.2011	0.077 0.0198	0.166	26.1% 1.2%	1.08 [0.78, 1.50]	
Kim,J.S.2010				1.02 [0.23, 4.52]	
N Engl J Med.1985	-0.0305 (7.6%	0.97 [0.53, 1.78]	
Peng,H.H.2019	-0.2614 (5.5%	0.77 [0.38, 1.56]	
Tveit, K. M.1997 Wu.J.X.2014	-0.5108 (0.3365 (8.6% 4.3%	0.60 [0.34, 1.06] 1.40 [0.63, 3.11]	
vvu.J.X.2014	0.3365	0.4074	4.3%	1.40 [0.63, 3.11]	
Total (95% CI)			100.0%	1.05 [0.89, 1.23]	• • • • • • • •
Heterogeneity: Chi ² = 7.2		$ ^2 = 0\%$		2	0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z	= 0.52 (P = 0.60)				Favours [experimental] Favours [control]

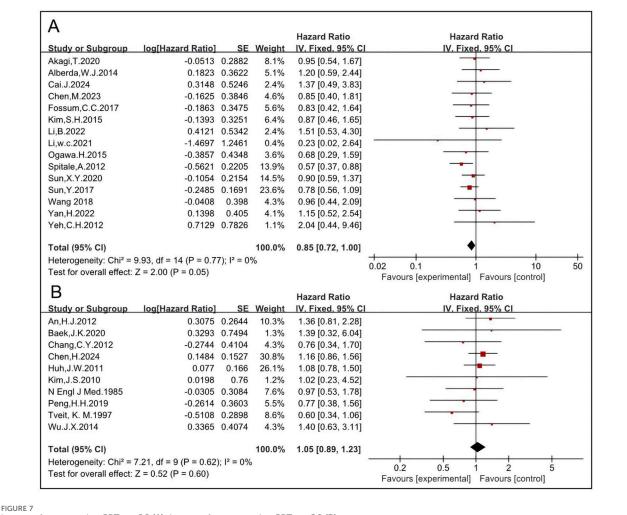
FIGURE 6

Impact of preoperative RT on OS (A). Impact of postoperative RT on OS (B).

23, 25, 28, 29, 30, 42, 49) (Figure 8), which is concordant with the results observed for postoperative RT mentioned above. SCRT was used without chemotherapy before surgical resection and eight studies, including 2,518 patients in the RT group and 2,596 in the non-RT group, were eligible (4, 11, 18, 24, 26, 35, 47, 55). The HR was 0.83 [95% CI: 0.76–0.90, P < 0.0001] (Figure 8). Taken together, these results indicate that both preoperative LCRT and preoperative SCRT significantly improve OS while postoperative LCRT might not.

3.1.6 RT may not improve OS of patients treated with TME

The impact of RT on OS in patients treated with TME was analyzed. Nineteen studies compared OS of patients receiving a combination of RT and TME vs. TME alone, and the pooled HR of was 1.02 [95% CI: 0.94–1.12, P = 0.59] (11, 12, 14, 18, 23, 27, 28, 29, 33, 41, 42, 45, 46, 49, 51, 52, 53, 55, 57) (Supplementary Figure S6). Nine studies, including 1,610 patients enrolled in the RT group and 1,981 in the non-RT group, were eligible to analyze the impact of preoperative RT (11, 14, 27, 33, 45, 51, 53, 55, 57). The HR was 1.00 [95% CI: 0.91–1.11, P = 0.93] (Figure 9). Preoperative LCCRT was employed in seven of nine studies. A total of 942 patients were enrolled in the RT group, while 1,088 patients were included in the non-RT group (11, 14, 27, 33, 45, 52, 55). The HR was 1.01 [95% CI: 0.91–1.12, P = 0.82]. Preoperative RT-alone was employed in two of nine studies. A total of 254 patients were enrolled in the RT group, while 467 patients were included in the non-RT group (51, 57). The HR was 0.88 [95% CI: 0.61–1.26, P = 0.47] (Figure 9). These results concordantly indicate that preoperative RT, regardless of the



Impact of preoperative CRT on OS (A). Impact of postoperative CRT on OS (B).

regimen used (including LCCRT or RT alone), may not improve OS of patients treated with TME.

Five studies were eligible to analyze the impact of postoperative RT on OS, with 454 patients enrolled in the RT group and 532 in the non-RT group (12, 23, 28, 29, 42). The HR was 1.18 [95% CI: 0.91–1.52, P = 0.20] (Figure 9). Taken together with the aforementioned data, these results concordantly indicate that RT, regardless of the regimen, may not improve OS of patients treated with TME, suggesting that RT may not be necessary.

3.1.7 Preoperative RT improves OS of patients treated with non-TME-only surgery

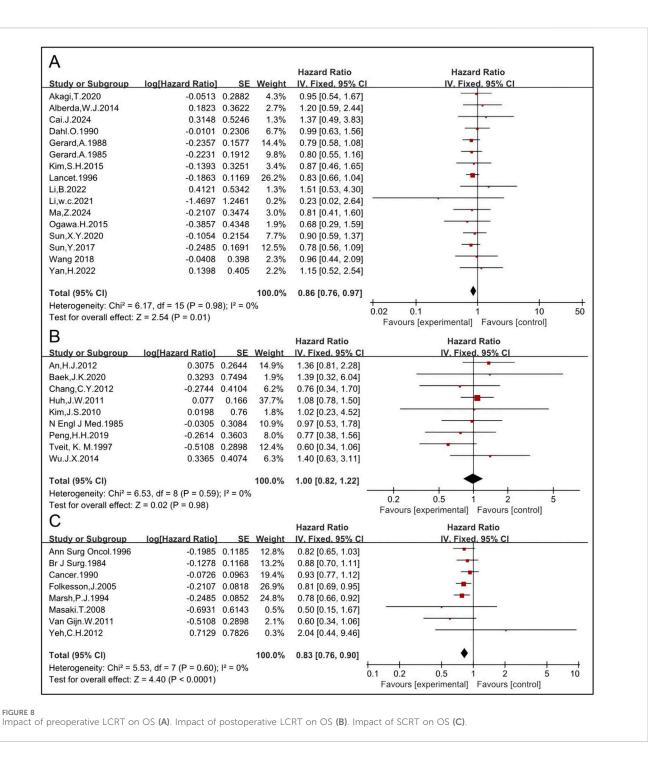
Nineteen studies enrolled 6,525 patients who underwent surgical treatment other than TME (non-TME-only). OS was compared between patients who received a combination of RT and non-TME-only surgery vs. those who underwent non-TME-only surgery alone (4, 5, 6, 15, 16, 17, 19, 24, 25, 26, 30, 31, 35, 36, 37, 43, 47, 50, 54). The pooled HR was 0.86 [95% CI: 0.81-0.92, P < 0.00001] (Supplementary Figure S7), indicating that RT significantly improves OS. Preoperative RT was employed in 16 trials, including 3,542 patients in the RT group and 3,854 in the non-RT group (4, 5, 6, 15, 16, 17, 19, 24, 26, 35, 36, 37, 46, 47, 50, 54). The HR was 0.85 [95% CI: 0.79-0.91, P < 0.00001]. Six

studies were eligible to analyze the impact of preoperative LCCRT on OS, and the HR was 0.77 [95% CI: 0.60–0.99, P = 0.04] (6, 19, 36, 43, 50, 54). Ten studies analyzed the effect of preoperative RT-alone on OS, and the HR was 0.86 [95% CI: 0.80–0.92, P < 0.0001] (4, 5, 15, 16, 17, 24, 26, 35, 37, 47) (Figure 10). Preoperative LCRT was employed in eight trials, and the HR was 0.84 [95% CI: 0.73–0.97, P = 0.02] (5, 6, 15, 16, 19, 37, 43, 54). Preoperative SCRT was employed in five trials, and the HR was 0.84 [95% CI: 0.77–0.91, P = <0.0001] (4, 24, 26, 35, 47) (Figure 10). These results concordantly indicate that each preoperative RT regimen, including LCCRT, RT-alone, LCRT, and SCRT, significantly improves OS of patients treated with non-TME-only surgery.

Postoperative RT was employed in three trials, including 181 patients in the RT group and 816 in the non-RT group (25, 30, 31). The HR was 1.08 [95% CI: 0.84–1.39, P = 0.57] (Supplementary Figure S7), indicating that postoperative RT may not improve OS of patients treated with non-TME-only surgery.

4 Discussion

The management of LARC requires a multidisciplinary approach, with treatment specific to each patient based on a



thorough assessment of disease risks. Multimodality treatment, along with the optimization of individual treatment components, have contributed to and improved prognosis (14, 31, 33, 57). At present, several MDT modalities are employed for LARC, with surgery playing a pivotal role. TME, combined with either preoperative RT or postoperative RT, is considered the gold standard surgery for the treatment of middle and low LARC. It is performed with precise dissection along an avascular, embryologically based plane, achieving good oncological and functional results (23, 32, 53). The supportive role of RT in patients treated with TME is challenged by, but not limited to, these three factors. First, low LR. Although several reliable clinic trials showed that RT significantly reduces LR by about 50% compared to TME alone, most of these trials were conducted more than 10 years ago (11, 12). Furthermore, those clinic trials conducted more than 10 years ago demonstrated that TME without RT alone results in a LR rate as low as about 10% (11, 12). Currently, mesorectal integrity is evaluated using high-resolution magnetic resonance imaging before surgery. When mesorectal integrity is used as the standard for evaluation, high-quality TME surgery results in a LR rate as low as 5% (32, 60). This raises the question of whether RT could further decrease the LR rate in

А

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio	Hazard Ratio
Alberda, W. J.2014		0.3622	2.0%	1.20 [0.59, 2.44]	
Cai, J.2024		0.5246	0.9%	1.37 [0.49, 3.83]	
			1.7%		
Chen,M.2023		0.3846		0.85 [0.40, 1.81]	
Li,B.2022		0.5342	0.9%	1.51 [0.53, 4.30]	
Sun,X.Y.2020		0.2154	5.6%	0.90 [0.59, 1.37]	
Sun,Y.2017	-0.2485		9.0%	0.78 [0.56, 1.09]	
Van Gijn.W.2011	0.0296	0.0576	77.8%	1.03 [0.92, 1.15]	
Wang 2018	-0.0408	0.398	1.6%	0.96 [0.44, 2.09]	
Yeh,C.H.2012	0.7129	0.7826	0.4%	2.04 [0.44, 9.46]	
Total (95% CI)			100.0%	1.00 [0.91, 1.11]	•
Heterogeneity: Chi ² =	4.88, df = 8 (P = 0.77); ² = 0%	,		
Test for overall effect:					0.01 0.1 1 10 10
	,				Favours [experimental] Favours [control]
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio
					IV. Fixed, 95% CI
		0.3622			IV. Fixed, 95% Cl
Alberda, W. J.2014	0.1823		2.1%	1.20 [0.59, 2.44]	IV. Fixed, 95% Cl
Alberda, W. J.2014 Cai,J.2024	0.1823 0.3148	0.5246	2.1% 1.0%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83]	IV. Fixed, 95% Cl
Alberda, W. J.2014	0.1823	0.5246 0.3846	2.1%	1.20 [0.59, 2.44]	IV. Fixed, 95% Cl
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023	0.1823 0.3148 -0.1625	0.5246 0.3846 0.5342	2.1% 1.0% 1.9%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81]	IV. Fixed, 95% Cl
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022	0.1823 0.3148 -0.1625 0.4121	0.5246 0.3846 0.5342 0.1691	2.1% 1.0% 1.9% 1.0%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30]	IV. Fixed, 95% Cl
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017	0.1823 0.3148 -0.1625 0.4121 -0.2485	0.5246 0.3846 0.5342 0.1691 0.0576	2.1% 1.0% 1.9% 1.0% 9.7%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09]	IV. Fixed. 95% Cl
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296	0.5246 0.3846 0.5342 0.1691 0.0576	2.1% 1.0% 1.9% 1.0% 9.7% 83.8%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15]	IV. Fixed, 95% Cl
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = 4	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12]	
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI)	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12]	
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = 4	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12]	
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = 4	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12]	
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = 4	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826 ; l ² = 0%	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12]	0.01 0.1 1 10 100 Favours [experimental] Favours [control]
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = - Test for overall effect: <u>Study or Subgroup</u> Ma,Z.2024	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (F = 0.60) Z = 0.23 (P = 0.82)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826 ; l ² = 0%	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5% 100.0%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12] Hazard Ratio IV, Fixed, 95% Cl 0.81 [0.40, 1.64]	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = - Test for overall effect: Study or Subgroup	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60) Z = 0.23 (P = 0.82)	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826 ; l ² = 0% <u>SE</u> 0.36	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5% 100.0%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12] Hazard Ratio IV, Fixed, 95% Cl	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio
Alberda, W. J.2014 Cai,J.2024 Chen,M.2023 Li,B.2022 Sun,Y.2017 Van Gijn.W.2011 Yeh,C.H.2012 Total (95% CI) Heterogeneity: Chi ² = - Test for overall effect: <u>Study or Subgroup</u> Ma,Z.2024	0.1823 0.3148 -0.1625 0.4121 -0.2485 0.0296 0.7129 4.59, df = 6 (P = 0.60) Z = 0.23 (P = 0.82) log[Hazard Ratio] -0.2107	0.5246 0.3846 0.5342 0.1691 0.0576 0.7826 ; l ² = 0% <u>SE</u> 0.36 0.2154	2.1% 1.0% 1.9% 1.0% 9.7% 83.8% 0.5% 100.0% Weight 26.4%	1.20 [0.59, 2.44] 1.37 [0.49, 3.83] 0.85 [0.40, 1.81] 1.51 [0.53, 4.30] 0.78 [0.56, 1.09] 1.03 [0.92, 1.15] 2.04 [0.44, 9.46] 1.01 [0.91, 1.12] Hazard Ratio IV, Fixed, 95% Cl 0.81 [0.40, 1.64]	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio

С

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio	1		Hazard Ratio		
An. H.J.2012	0.3075	0.2644	23.8%	1.36 [0.81, 2.28]					
Beak, J.K.2020	0.3293	0.7494	3.0%	1.39 [0.32, 6.04]					
Huh, J.W.2011	0.077	0.166	60.4%	1.08 [0.78, 1.50]			-		
Kim, J.S.2010	0.0198	0.76	2.9%	1.02 [0.23, 4.52]		0		4.9%	
Wu,J,X.2014	0.3365	0.4074	10.0%	1.40 [0.63, 3.11]					
Total (95% CI)			100.0%	1.18 [0.91, 1.52]			•		
Heterogeneity: Chi ² =	0.83, df = 4 (P = 0.93)); 2 = 0%	, ,					10	400
Test for overall effect:	Z = 1.27 (P = 0.20)	Course Editoria			0.01 Favours	0.1 s [experime	ental] Favou	10 Irs [control]	100

01 0.1 1 10 Favours [experimental] Favours [control]

FIGURE 9

Impact of preoperative RT on OS of patients treated with TME (A). Impacts of preoperative CRT and preoperative RT-alone on OS in patients treated with TME (B). Impact of postoperative RT on OS in patients treated with TME (C).

patients treated with TME. An updated meta-analysis was conducted to evaluate the impact of RT on LR in LARC patients treated with TME. Data showed that neither preoperative nor

Test for overall effect: Z = 0.72 (P = 0.47)

postoperative RT significantly reduced LR. Second, there is a risk of RT-related complications, morbidities, and mortality (14, 26). RT can lead to complications such as enteritis, wound sepsis,

tudy or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed, 95% CI	Hazard IV. Fixed	1. 95% CI	
6.1 CRT	Contraction of Long (A)				11.11/140		
kagi,T.2020	-0.0513	0.2882	1.4%	0.95 [0.54, 1.67]			
sum,C.C.2017	-0.1863		1.0%	0.83 [0.42, 1.64]		-	
m,S.H.2015	-0.1393		1.1%	0.87 [0.46, 1.65]			
gawa.H.2015	-0.3857	0.4348	0.6%	0.68 [0.29, 1.59]		_	
itale,A.2012	-0.5621	0.2205	2.4%	0.57 [0.37, 0.88]			
in,H.2022	0.1398	0.405	0.7%	1.15 [0.52, 2.54]	-		
ibtotal (95% CI)			7.3%	0.77 [0.60, 0.99]	•		
eterogeneity: Chi ² = 3 est for overall effect: 2	.64, df = 5 (P = 0.60); 2 = 2.07 (P = 0.04)	$1^2 = 0\%$					
6.2 RT-along							
n Surg Oncol 1996	-0.1985	0.1185	8.4%	0.82 [0.65, 1.03]	-		
J Surg.1984	-0.1278	0.1158	8.7%	0.88 [0.70, 1.11]	-		
incer.1990	-0.0726	0.0963	12.7%	0.93 [0.77, 1.12]	-	-	
hl.O.1990	-0.0101	0.2306	2.2%	0.99 [0.63, 1.56]		_	
Ikesson, J.2005	-0.2107	0.0818	17.6%	0.81 [0.69, 0.95]	-		
erard, A.1985	-0.2231		3.2%	0.80 [0.55, 1.16]		-	
erard A.1988	-0.2357		4.7%	0.79 [0.58, 1.08]	-		
oldberg, P.A. 1994		0.1078	10.2%	1.05 [0.85, 1.30]			
ncet.1996	-0.1863		8.6%	0.83 [0.66, 1.04]			
arsh, P.J. 1994	-0.2485	0.0852	16.3%	0.78 [0.66, 0.92]			
ubtotal (95% Cl) aterogeneity: Chi ² = 7	.02, df = 9 (P = 0.64);	12 = 0.04	92.7%	0.86 [0.80, 0.92]			
	r = 4.36 (P < 0.0001)	1 0.76					
tal (95% CI)			100.0%	0.85 [0.79, 0.91]	•		
	1.32, df = 15 (P = 0.7	3); l ² = 0 ⁴			0.02 0.1	10	50
est for overall effect: 2	2 = 4.76 (P < 0.00001))			Favours [experimental]		00
est for subaroup differ	ences: Chi ² = 0.66. df	f=1(P=	0.42). I ^z =	• 0%	, a caro (cabo munu)		
	ences: Chi ² = 0.66. df	f = 1 (P =	0.42). I ^z =	Hazard Ratio		d Ratio	
udy or Subgroup	ences: Ch ² = 0.66. df log[Hazard Ratio]		(0.42), I ² =		Hazar		
udy or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed, 95% CI	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT ragi.T.2020	log[Hazard Ratio]	SE 0.2882	Weight	Hazard Ratio	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (agi,T.2020	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed, 95% CI	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT agi,T.2020 ahl.C.1990	<u>log[Hazard Ratio]</u> -0.0513 -0.0101	SE 0.2882	Weight	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT ragi,T.2020 shi,C.1990 erard,A.1985	log[Hazard Ratio] -0.0513 -0.0101 -0.2231	0.2882 0.2306	Weight 1.6% 2.6%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (rag), T.2020 ahl.C.1990 erard, A.1985 erard, A.1988	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357	0.2882 0.2306 0.1912	Weight 1.6% 2.6% 3.7%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (ag), T.2020 ahl.O.1990 erarc, A.1985 erard, A.1986 m, S.H.2015	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393	0.2882 0.2306 0.1912 0.1577	Weight 1.6% 2.6% 3.7% 5.5%	Hazard Ratio IV, Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (agi,T.2020 ahl.C.1990 erard,A.1985 erard,A.1986 erard,A.1986 mr.S.H.2015 incet.1996	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863	0.2882 0.2306 0.1912 0.1577 0.3251	Weight 1.6% 2.6% 3.7% 5.5% 1.3%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04]	Hazar	d Ratio	
And the second s	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863 -0.3857	SE 0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.79 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (ag), T.2020 ahl.O.1990 erarci, A.1985 erarci, A.1985 erarci, A.1986 m, S.H.2015 ancet. 1996 gewa, H.2015 an, H.2022	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863 -0.3857	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 0.8%	Hazard Ratio IV. Fixed, 95% CI 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (ag),T.2020 ahl.O.1990 erard,A.1985 erard,A.1988 m,S.H.2015 incet.1996 gava.H.2015 an,H.2022 ubtotal (95% Cl) eterogeneity: Chi ² = 1	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863 -0.3857 -0.1398 1.76, df = 7 (P = 0.97)	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.79 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59]	Hazar	d Ratio	
tudy or Subgroup 7.1 LCRT (ag), T. 2020 ahl. O. 1990 erard, A. 1985 erard, A. 1985 erard, A. 1986 m, S. H. 2015 an, H. 2022 ubtotal (95% Cl) eterogeneity: Chi ² = 1	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863 -0.3857 -0.1398 1.76, df = 7 (P = 0.97)	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 0.8%	Hazard Ratio IV. Fixed, 95% CI 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54]	Hazar	d Ratio	
Audy or Subgroup 7.1 LCRT (ag),T.2020 ahl.0.1990 erarc,A.1985 erard,A.1985 erard,A.1986 m,S.H.2015 ancet.1996 gawa.H.2015 an,H.2022 ubtotal (95% CI) eterogeneity: Chi ² = 1 est for overall effect :	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863 -0.3857 -0.1398 1.76, df = 7 (P = 0.97)	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 0.8%	Hazard Ratio IV. Fixed, 95% CI 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (rag), T.2020 erard, A.1985 erard, A.1985 erard, A.1988 m,S.H.2015 erard, A.1988 m,S.H.2015 erard, A.1996 gewa, H.2015 an, H.2022 ubtotal (95% CI) eterogeneity: Chi ² = 1 est for overall effect; 2 7.2 SCRT	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1363 -0.3657 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02)	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 0.8%	Hazard Ratio IV. Fixed, 95% CI 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54]	Hazar	d Ratio	
And the set of the set	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.1863 -0.3857 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02) -0.1985	5E 0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; ² = 0%	Weight 1.6% 2.6% 5.5% 1.3% 10.0% 0.7% 0.8% 26.3%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.79 [0.58, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97]	Hazar	d Ratio	
And the set of the set	log[Hazard Ratio] -0.0513 -0.0101 -0.2237 -0.1393 -0.1863 -0.3857 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02) -0.1985 -0.1278	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; l ² = 0% 0.1185	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 26.3% 9.7%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (agi,T.2020) ahl.0.1990 erard,A.1985 erard,A.1986 erard,A.1986 m,S.H.2015 an,H.2015 an,H.2015 an,H.2022 ubtotal (95% CI) eterogeneity: Chi ² = 1 ssi for overall effect : 7.2 SCRT an Surg Oncol.1996 J Surg.1984 ancer.1990	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.3857 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02) -0.1985 -0.1278 -0.0726	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; I ² = 0% 0.1185 0.1168 0.0963	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.8% 26.3% 9.7% 10.0% 1	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.82 [0.65, 1.03] 0.88 [0.70, 1.11] 0.93 [0.77, 1.12]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT ragi, T.2020 ahl, C.1990 erarci, A.1985 erard, E.2015 erard, E.20	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.3857 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02) -0.1985 -0.1278 -0.0726 -0.2107	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; I ² = 0% 0.1185 0.1185 0.1188 0.0963 0.0818	Weight 1.6% 2.6% 5.5% 1.3% 10.0% 0.7% 0.8% 26.3% 9.7% 10.0% 14.7% 20.4%	Hazard Ratio IV. Fixed, 95% CI 0.99 [0.63, 1.56] 0.99 [0.63, 1.56] 0.79 [0.58, 1.08] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.84 [0.73, 0.97] 0.88 [0.70, 1.11] 0.93 [0.77, 1.12] 0.81 [0.69, 0.95]	Hazar	d Ratio	
udy or Subgroup 7.1 LCRT (ag), T.2020 ahl.0.1990 erarc, A.1985 erard, A.1985 erard, A.1986 m, S.H.2015 inset.1996 gawa.H.2015 inst.1996 gawa.H.2015 inst.1996 J.Strogeneity: Chi ² = 1 for overall effect; 3 7.2 SCRT an Surg Oncol.1996 J.J.Surg.1984 ancer.1990 Skesson J.2005 arsh, P.J.1994	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.3857 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02) -0.1985 -0.1278 -0.0726 -0.2107	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; I ² = 0% 0.1185 0.1185 0.1188 0.0963 0.0818	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 26.3% 9.7% 10.0% 14.7% 20.4% 18.8%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.84 [0.73, 0.97] 0.88 [0.70, 1.11] 0.93 [0.77, 1.12] 0.81 [0.69, 0.95] 0.78 [0.66, 0.92]	Hazar	d Ratio	
And the set of the set	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.3857 0.1398 1.76, df = 7 (P = 0.97) Z = 2.34 (P = 0.02) -0.1985 -0.1278 -0.0726 -0.2107	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; l ² = 0% 0.1185 0.1168 0.0963 0.0818 0.0852	Weight 1.6% 2.6% 3.7% 5.5% 1.3% 10.0% 0.7% 26.3% 9.7% 10.0% 14.7% 20.4% 18.8%	Hazard Ratio IV. Fixed, 95% CI 0.99 [0.63, 1.56] 0.99 [0.63, 1.56] 0.79 [0.58, 1.08] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.84 [0.73, 0.97] 0.88 [0.70, 1.11] 0.93 [0.77, 1.12] 0.81 [0.69, 0.95]	Hazar	d Ratio	
And the set of the set	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.3857 -0.3857 -0.3857 -0.3857 -0.3985 -0.2107 -0.2178 -0.0726 -0.2107 -0.2485 2.26, df = 4 (P = 0.69)	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; l ² = 0% 0.1185 0.1168 0.0963 0.0818 0.0852	Weight 1.6% 2.6% 5.5% 1.3% 10.0% 0.7% 26.3% 9.7% 10.0% 14.7% 26.4% 14.7% 14.7% 14.8% 73.7%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.79 [0.58, 1.08] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.84 [0.73, 0.97] 0.84 [0.70, 1.11] 0.93 [0.77, 1.12] 0.81 [0.69, 0.95] 0.78 [0.66, 0.92] 0.84 [0.77, 0.91]	Hazar	d Ratio	
Andy or Subgroup 7.1 LCRT (ag), T.2020 ahl.0.1990 erard, A.1985 erard, A.1985 erard, A.1986 m,S.H.2015 an, H.2025 ubtotal (95% Cl) eterogeneity: Chi ² = 1 and Surg Oncol.1996 J. Surg.1984 ancer.1990 Jikesson J.2005 arsh, P.J.1994 ubtotal (95% Cl) eterogeneity: Chi ² = 2 est for overall effect; 2 arsh, P.J.1994 ubtotal (95% Cl)	$\begin{array}{c} & -0.0513 \\ & -0.0513 \\ & -0.011 \\ & -0.2231 \\ & -0.2357 \\ & -0.2357 \\ & -0.1393 \\ & -0.1863 \\ & -0.3857 \\ & 0.1398 \\ \hline \\ 1.76, df = 7 (P = 0.97) \\ Z = 2.34 (P = 0.02) \\ & -0.1985 \\ & -0.1278 \\ & -0.0726 \\ & -0.2107 \\ & -0.2485 \\ \hline \\ 2.26, df = 4 (P = 0.69) \\ Z = 4.16 (P < 0.0001) \end{array}$	0.2882 0.2306 0.1912 0.1577 0.3251 0.1169 0.4348 0.405 ; I ² = 0% 0.1185 0.1168 0.08512 ; I ² = 0%	Weight 1.6% 2.6% 3.7% 1.3% 10.0% 0.7% 0.8% 26.3% 9.7% 10.0% 14.7% 20.4% 18.8% 73.7% 100.0%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.80 [0.55, 1.16] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.84 [0.73, 0.97] 0.88 [0.70, 1.11] 0.93 [0.77, 1.12] 0.81 [0.69, 0.95] 0.78 [0.66, 0.92]	Hazar	d Ratio	
Antipy of Subgroup 7.1 LCRT (agi),T.2020 ahi,C.1990 erard,A.1985 erard,A.1985 erard,A.1985 erard,A.1985 gewa.H.2015 an,H.2022 ubtotal (95% CI) eterogeneity: Chi ² = 1 5.1 Surg.1984 ancer.1990 bikesson J.2005 arsh,P.J.1994 ubtotal (95% CI) eterogeneity: Chi ² = 2 est for overall effect 2 batal (95% CI) eterogeneity: Chi ² = 4	log[Hazard Ratio] -0.0513 -0.0101 -0.2231 -0.2357 -0.1393 -0.3857 -0.3857 -0.3857 -0.3857 -0.3985 -0.2107 -0.2178 -0.0726 -0.2107 -0.2485 2.26, df = 4 (P = 0.69)	SE 0.2882 0.2306 0.1912 0.1577 0.3251 0.4348 0.405 ; l ² = 0% 0.1185 0.1168 0.0963 0.0818 0.0852 ; l ² = 0% 3); l ² = 0%	Weight 1.6% 2.6% 3.7% 1.3% 10.0% 0.7% 0.8% 26.3% 9.7% 10.0% 14.7% 20.4% 18.8% 73.7% 100.0%	Hazard Ratio IV. Fixed, 95% CI 0.95 [0.54, 1.67] 0.99 [0.63, 1.56] 0.79 [0.58, 1.08] 0.79 [0.58, 1.08] 0.87 [0.46, 1.65] 0.83 [0.66, 1.04] 0.68 [0.29, 1.59] 1.15 [0.52, 2.54] 0.84 [0.73, 0.97] 0.84 [0.73, 0.97] 0.84 [0.70, 1.11] 0.93 [0.77, 1.12] 0.81 [0.69, 0.95] 0.78 [0.66, 0.92] 0.84 [0.77, 0.91]	Hazar	d Ratio	

FIGURE 10

Impacts of preoperative CRT and preoperative RT-alone on OS in patients treated with non-TME sugery (A). Impacts of preoperative LCRT and preoperative SCRT on OS in patients treated with non-TME sugery (B).

anastomotic leak, among others. It has been reported that 90% of patients receiving pelvic RT experience chronic changes in their bowel habits, with half reporting a reduced quality of life attributable to these symptoms (61). RT-related complications not only cause a very negative impact on the quality of life but also increase the economic burden. Third, there is no observed benefit in OS. Survival is the most important endpoint in the treatment of rectal cancer. Data indicate that there was no significant difference in OS between

the group receiving the combination of TME and RT and the TMEalone group. Further analysis indicates that neither preoperative RT nor postoperative RT benefits OS (Figure 8). Postoperative radiotherapy is not recommended for LARC by certain guidelines. However, it is not uncommon for a patient to be misdiagnosed with early-stage rectal cancer before surgery, only to be diagnosed as LARC after surgery. Under this condition, postoperative radiotherapy is recommended by certain guidelines. Therefore, it may not be meaningless to discuss the role of postoperative radiotherapy. However, our results showed that postoperative radiotherapy did not improve the survival rate in patients with colorectal cancer, suggesting that caution should be exercised when considering its use. The HRs for preoperative RT, postoperative RT, and the combination of pre- and postoperative RT are all greater than one, indicating that the three RT groups had a shorter OS compared to the TME-alone group, although this difference was not statistically significant.

Therefore, preoperative RT or postoperative RT may not be necessary for all patients with completely resected LARC. RT might be cautiously recommended for a few patients at high risk. Factors such as mesorectal integrity, T stage, lymph node status, lesion location, among others, are considered in patient selection. Unfortunately, only a few studies have thoroughly explored the roles of these factors and further research is needed (31, 62, 63). Due to the high risk of surgeryrelated complications, morbidities, and mortality associated with TME-for example, an increased risk of anastomotic fistula with an incidence of about 11%-18% (64, 65)-a considerable number of patients undergo non-TME-only surgery (31, 66). Postoperative complications of colorectal cancer mainly include anastomotic leakage, bleeding, intestinal obstruction, surgical site infection, deep vein thrombosis, and other related conditions. These complications seriously affect the quality of life of patients, increase pain and length of hospital stay, and, in severe cases, can be life-threatening (67). Recently, it has been shown that changes in butyrylcholinesterase levels during colorectal surgery may be associated with the occurrence of complications, and monitoring these levels could potentially aid in the early prediction and intervention of postoperative complications (68). Currently, lateral lymph nodes are also considered potential sites of local lesions and should be managed with lateral lymph node dissection. Studies have shown that pelvic lymph node dissection guided by NIR fluorescence imaging is feasible. From the number of lymph nodes and postoperative outcomes, the technique demonstrates good performance, suggesting potential advantages in surgical efficacy and postoperative recovery. It is a technique worthy of attention (69). Data indicate that preoperative RT significantly benefits patients treated with non-TME-only surgery in terms of LR and OS (Figures 9, 10). Clinically, neoadjuvant chemoradiotherapy has become the standard treatment for LARC, achieving a high anal sphincter preservation rate. In some reports, this preservation rate can reach as high as 85.2%. However, the ultimate success of preserving the anal sphincter is also influenced by factors such as tumor location, stage, the patient's physical condition, and other variables. According to the literature, further investigations have been conducted into the potential clinical application of deep learning algorithms for the classification and diagnosis of CRC histopathology images. The advancements made possible by deep learning algorithms have the potential to improve the accuracy and efficacy of CRC detection (70, 71). In recent decades, different RT regimens, including LCCRT and SCRT, have been applied to treat LARC. CRT tends to yield better survival outcomes than RT alone in certain types of cancers. A few trials have reported that LCCRT yielded a higher rate of pCR, lower LR rates, and reduced T and N stages compared to SCRT (72, 73). The impact of different RT regimens on OS was analyzed. Preoperative RT alone, preoperative CRT, preoperative LCCRT, and preoperative SCRT all benefit patients treated with non-TME-only surgery in terms of OS (Figure 10). Therefore, preoperative RT is essential for patients with completely resected middle and low LARC. The data here show that postoperative RT did not improve OS (Figure 4). This suggests that postoperative RT may not be necessary for all patients with completely resected LARC. Postoperative RT may be cautiously recommended for selected high-risk patients.

Over two decades ago, meta-analyses showed that postoperative RT had no impact on survival, while preoperative RT had a significant positive effect (74, 75). At present, modern precision radiotherapy techniques, such as 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), are widely used. These techniques allow for the delivery of high radiation doses to the gross tumor, bulky lymph nodes, and high-risk areas, while minimizing the dose and preserving the volume of organs at risk (76). Nevertheless, the conclusion of this updated meta-analysis remains unchanged. Postoperative RT does not benefit patients in terms of OS, while preoperative RT significantly improves OS (Figures 4–6). Further analysis suggests that the effect of preoperative RT may be attributable to its impact on patients who underwent non-TME-only surgery, rather than those who received TME.

In addition to the inherent limitations of individual trials, there are also limitations to our analyses. First, treatment modalities vary considerably among different clinic trials. Different chemotherapy regimens were employed in different clinic trials, and even within a single trial. Some patients received chemoradiotherapy, while others received RT alone. Additionally, different RT techniques were used. These factors pose a significant risk of bias in the implementation of the meta-analysis. Second, patients with different T-stages and different lymph node statuses were included. The tumor's biological heterogeneity and perineural and vascular invasion in different patients were not considered. Different patients have varying risks of LR, and RT might benefit patients with different risks profiles in distinct ways. These confounders affect the efficacy of RT more or less. Third, the sample sizes in different trials vary considerably. Without considering the impact of differences in TME resection techniques on surgical outcomes and patient prognosis, variations in the TME techniques employed by different operators may result in different margin statuses, LR rates, and other outcomes. Fourth, some database, such as Web of Science and others, were not included in the search due to limited access. Because of limitations, data should be interpreted with caution. Clinicians should carefully evaluate the indications to ensure favorable oncological outcomes and inform patients about the potential risks to functional outcomes.

5 Conclusion

Preoperative RT, regardless of the regimen, benefits LARC patients treated with non-TME-only surgery in terms of OS, while preoperative RT does not improve OS in patients treated with TME. Postoperative RT does not improve OS in patients with completely resected LARC. Due to these limitations, data should be interpreted with caution.

Author contributions

WW: Data curation, Methodology, Visualization, Writing – original draft, Writing – review and editing. RZ: Data curation, Methodology, Writing – review and editing. XL: Methodology, Writing – original draft, Writing – review and editing. ML: Writing – original draft. HB: Writing – original draft. JG: Writing – original draft. BY: Writing – original draft. ZZ: Conceptualization, Investigation, Writing – original draft, Writing – review and editing. JH: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This manuscript was funded by Hebei Administration of Traditional Chinese Medicine (2023020).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer J clinicians* (2024) 74(3):229–63. doi:10.3322/ caac.21834

2. He J, Shin H, Wei X, Kadegowda AKG, Chen R, Xie SK. NPC1L1 knockout protects against colitis-associated tumorigenesis in mice. *BMC Cancer* (2015) 15:189. doi:10. 1186/s12885-015-1230-0

3. Huang J, Li H, Wang X, Liang X, Zhao T, Hu J, et al. Impacts of ezetimibe on risks of various types of cancers: a meta-analysis and systematic review. *Eur J Cancer Prev* (2023) 32(1):89–97. doi:10.1097/CEJ.000000000000750

4. Stockholm Rectal Cancer Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma: a prospective randomized trial. *Cancer.* (1990) 66(1): 49–55. doi:10.1002/1097-0142(19900701)66.1<4910.1002/1097-0142(19900701)66: 1<49::aid-cncr2820660111>3.0.co;2-1aid-cncr2820660111>3.0.co

5. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. Medical Research Council Rectal Cancer Working Party. *Lancet (London, England)* (1996) 348(9042):1605–10. doi:10. 1016/s0140-6736(96)05348-2

6. Akagi T, Inomata M, Fujishima H, Fukuda M, Konishi T, Tsukamoto S, et al. Preoperative chemoradiotherapy versus surgery alone for advanced low rectal cancer: a large multicenter cohort study in Japan. *Surg Today* (2020) 50(11):1507–14. doi:10. 1007/s00595-020-02034-2

7. Musio D, De Felice F, Magnante AL, Ciolina M, De Cecco CN, Rengo M, et al. Diffusion-weighted magnetic resonance application in response prediction before, during, and after neoadjuvant radiochemotherapy in primary rectal cancer carcinoma. *Biomed Research International* (2013) 2013:1–5. doi:10.1155/2013/740195

8. Oey O, Lin CP, Khattak MA, Ferguson T, Theophilus M, Tiong SS, et al. Total neoadjuvant therapy in locally advanced rectal cancer: insights from the western Australian context. *Diseases (Basel, Switzerland)* (2024) 12(10):257. doi:10.3390/diseases12100257

9. Benson AB, Venook AP, Adam M, Chang G, Chen YJ, Ciombor KK, et al. NCCN Guidelines[®] insights: rectal cancer, version 3.2024. *J Natl Compr Cancer Netw* (2024) 22(6):366–75. doi:10.6004/jnccn.2024.0041

10. Musio D, De Felice F, Bulzonetti N, Guarnaccia R, Caiazzo R, Bangrazi C, et al. Neoadjuvant-intensified treatment for rectal cancer: time to change? *World J Gastroenterol* (2013) 19(20):3052–61. doi:10.3748/wjg.v19.i20.3052

11. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EMK, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *The Lancet Oncol* (2011) 12(6):575–82. doi:10.1016/s1470-2045(11)70097-3

12. Huh JW, Lim SW, Kim HR, Kim YJ. Effects of postoperative adjuvant radiotherapy on recurrence and survival in stage III rectal cancer. J Gastrointest Surg (2011) 15(6):963–70. doi:10.1007/s11605-011-1497-7

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/or.2025.1567818/ full#supplementary-material

13. Li H, Che K, Zhi Z, Xu W, Huang J, Wang X, et al. Efficacy and safety of methylphenidate and ginseng in cancer-related fatigue: a network meta-analysis of randomized controlled trials. *Translational Cancer Res* (2023) 12(4):732–42. doi:10. 21037/tcr-22-2303

14. Cai J, Lin K, Luo T, Weng J, Liu H, Yuan Z, et al. Neoadjuvant chemotherapy is noninferior to chemoradiotherapy for early-onset locally advanced rectal cancer in the FOWARC trial. *Br J Cancer* (2024) 130(9):1434–40. doi:10.1038/s41416-024-02652-4

15. Dahl O, Horn A, Morild I, Halvorsen JF, Odland G, Reinertsen S, et al. Lowdose preoperative radiation postpones recurrences in operable rectal cancer: results of a randomized multicenter trial in western Norway. *Cancer* (1990) 66(11):2286-94. doi:10.1002/1097-0142(19901201)66:11<2286::aidcncr2820661106>3.0.co;2-t

16. Gerard A, Berrod JL, Pene F, Loygue J, Laugier A, Bruckner R, et al. Interim analysis of a phase III study on preoperative radiation therapy in resectable rectal carcinoma. Trial of the gastrointestinal tract cancer cooperative group of the European organization for research on treatment of cancer (EORTC). *Cancer* (1985) 55(10): 2373–9. doi:10.1002/1097-0142(19850515)55:10<2373:aid-cncr2820551012>3.0.co; 2-d

17. Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey J. Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer (Oxford, Engl : 1990)* (1994) 30(11):1602–6. doi:10.1016/0959-8049(94)00312-s

18. Masaki T, Takayama M, Matsuoka H, Abe N, Ueki H, Sugiyama M, et al. Intraoperative radiotherapy for oncological and function-preserving surgery in patients with advanced lower rectal cancer. *Langenbeck's Arch Surg* (2008) 393(2):173–80. doi:10.1007/s00423-007-0260-8

19. Ogawa H, Uemura M, Nishimura J, Hata T, Ikenaga M, Takemasa I, et al. Preoperative chemoradiation followed by extensive pelvic surgery improved the outcome of posterior invasive locally recurrent rectal cancer without deteriorating surgical morbidities: a retrospective, single-institution analysis. *Ann Surg Oncol* (2015) 22(13):4325-34. doi:10.1245/s10434-015-4452-0

20. Pacelli F, Di Giorgio A, Papa V, Tortorelli AP, Covino M, Ratto C, et al. Preoperative radiotherapy combined with intraoperative radiotherapy improve results of total mesorectal excision in patients with T3 rectal cancer. *Dis Colon and Rectum* (2004) 47(2):170–9. doi:10.1007/s10350-003-0028-3

21. Räsänen M, Renkonen-Sinisalo L, Mustonen H, Lepistö A. Is there a need for neoadjuvant short-course radiotherapy in T3 rectal cancer with positive lymph node involvement? A single-center retrospective cohort study. *World J Surg Oncol* (2019) 17(1):139. doi:10.1186/s12957-019-1670-0

22. Tveit KM, Guldvog I, Hagen S, Trondsen E, Harbitz T, Nygaard K, et al. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer: Adjuvant Treatment Of Rectal Cancer. Br J Surg (1997) 84(8):1130–5. doi:10.1046/j.1365-2168.1997.02863.x

23. Wu JX, Wang Y, Chen N, Chen L, Bai P, Pan J. In the era of total mesorectal excision: adjuvant radiotherapy may be unnecessary for pT3N0 rectal cancer. *Radiat Oncol (London, England)* (2014) 9:159. doi:10.1186/1748-717x-9-159

24. Duncan W, Smith AN, Freedman LS, Alderson MR, Arnott SJ, Bleehen NM, et al. The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial. *J Br Surg* (1984) 71(1):21–5. doi:10. 1002/bjs.1800710107

25. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. *New Engl J Med* (1985) 312(23):1465–72. doi:10. 1056/nejm198506063122301

26. Cedermark B. Randomized study on preoperative radiotherapy in rectal carcinoma. Ann Surg Oncol (1996) 3(5):423–30. doi:10.1007/bf02305759

27. Alberda WJ, Verhoef C, Nuyttens JJ, Rothbarth J, van Meerten E, de Wilt JHW, et al. Outcome in patients with resectable locally recurrent rectal cancer after total mesorectal excision with and without previous neoadjuvant radiotherapy for the primary rectal tumor. *Ann Surg Oncol* (2014) 21(2):520–6. doi:10.1245/s10434-013-3306-x

28. An HJ, Yu CS, Yun SC, Kang BW, Hong YS, Lee JL, et al. Adjuvant chemotherapy with or without pelvic radiotherapy after simultaneous surgical resection of rectal cancer with liver metastases: analysis of prognosis and patterns of recurrence. *Int J Radiat Oncol Biol Phys* (2012) 84(1):73–80. doi:10.1016/j.ijrobp.2011.10.070

29. Baek JY, Yu JI, Park HC, Choi DH, Yoo GS, Lee WY, et al. Determining whether postoperative chemoradiotherapy is required in patients with pathologic T3N0 rectal cancer with negative resection margin. *Int J colorectal Dis* (2020) 35(12):2239–48. PubMed PMID: 32734414; eng. doi:10.1007/s00384-020-03701-z

30. Chang CY, Kim HC, Park YS, Park JO, Choi DH, Park HC, et al. The effect of postoperative pelvic irradiation after complete resection of metastatic rectal cancer. *J Surg Oncol* (2012) 105(3):244–8. PubMed PMID: 21987401; eng. doi:10.1002/jso. 22109

31. Chen H, Hu D, Su W, Li S, Zhang G, Si X, et al. Endoscopic resection vs. endoscopic resection plus chemoradiation for T1 stage colorectal cancer: a real-world retrospective cohort study. *Translational Cancer Res* (2024) 13(2):989–98. PubMed PMID: 38482418; PubMed Central PMCID: PMCPMC10928597. eng. doi:10.21037/ttr-23-1411

32. Chen JH, Ye Q, Huang F. Determining the survival benefit of postoperative radiotherapy in patients with pT1-3N1M0 rectal cancer undergoing total mesorectal excision: a retrospective analysis. *BMC Gastroenterol* (2023) 23(1):83. PubMed PMID: 36959560; PubMed Central PMCID: PMCPMC10037866. eng. doi:10.1186/s12876-023-02697-4

33. Chen M, Ma Y, Song YW, Huang J, Gao Y, Zheng J, et al. Survival outcomes of different neoadjuvant treatment regimens in patients with locally advanced rectal cancer and MRI-detected extramural venous invasion. *Cancer Med* (2023) 12(21): 20523–37. PubMed PMID: 37864414; PubMed Central PMCID: PMCPMC10660615. eng. doi:10.1002/cam4.6625

34. Cho SH, Choi GS, Kim GC, Seo AN, Kim HJ, Kim WH, et al. Long-term outcomes of surgery alone versus surgery following preoperative chemoradiotherapy for early T3 rectal cancer: a propensity score analysis. *Medicine* (2017) 96(12):e6362. PubMed PMID: 28328820; PubMed Central PMCID: PMCPMC5371457. eng. doi:10.1097/md. 000000000006662

35. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* (2005) 23(24):5644–50. PubMed PMID: 16110023; eng. doi:10.1200/jco.2005.08.144

36. Fossum CC, Alabbad JY, Romak LB, Hallemeier CL, Haddock MG, Huebner M, et al. The role of neoadjuvant radiotherapy for locally-advanced rectal cancer with resectable synchronous metastasis. *J Gastrointest Oncol* (2017) 8(4):650–8. PubMed PMID: 28890815; PubMed Central PMCID: PMCPMC5582044. eng. doi:10.21037/jgo. 2017.06.07

37. Gérard A, Buyse M, Nordlinger B, Loygue J, Pène F, Kempf P, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Ann Surg* (1988) 208(5):606–14. PubMed PMID: 3056288; PubMed Central PMCID: PMCPMC1493780. eng. doi:10.1097/00000658-198811000-00011

38. Huang YX, Lin YZ, Li JL, Zhang X, Tang L, Zhuang Q, et al. Role of postoperative radiotherapy in pT3N0 rectal cancer: a risk-stratification system based on population analyses. *Cancer Med* (2019) 8(3):1024–33. PubMed PMID: 30714683; PubMed Central PMCID: PMCPMC6434337. eng. doi:10.1002/cam4.1991

39. Joye I, Silversmit G, Van Eycken E, Debucquoy A, Vandendael T, Penninckx F, et al. Survival among clinical stage I-III rectal cancer patients treated with different preoperative treatments: a population-based comparison. *Cancer Epidemiol* (2016) 43: 35–41. PubMed PMID: 27388565; eng. doi:10.1016/j.canep.2016.06.007

40. Kang BM, Baek JH, Park SJ, Baek SK, Park KJ, Choi HJ, et al. Impact of adjuvant therapy type on survival in stage II/III rectal cancer without preoperative chemoradiation: a Korean multicenter retrospective study. *Ann Coloproctol* (2018) 34(3):144–51. PubMed PMID: 29991203; PubMed Central PMCID: PMCPMC6046544. eng. doi:10.3393/ac.2017.09.26.1

41. Kim JC, Takahashi K, Yu CS, Kim HC, Kim TW, Ryu MH, et al. Comparative outcome between chemoradiotherapy and lateral pelvic lymph node dissection

following total mesorectal excision in rectal cancer. Ann Surg (2007) 246(5):754–62. PubMed PMID: 17968166; eng. doi:10.1097/SLA.0b013e318070d587

42. Kim JS, Kim NK, Min BS, Hur H, Ahn JB, Keum KC. Adjuvant radiotherapy following total mesorectal excision for stage IIA rectal cancer: is it beneficial? *Int J colorectal Dis* (2010) 25(9):1103–10. PubMed PMID: 20544208; eng. doi:10.1007/s00384-010-0970-1

43. Kim SH, Kim JH, Jung SH. Comparison of oncologic outcomes of metastatic rectal cancer patients with or without neoadjuvant chemoradiotherapy. *Int J colorectal Dis* (2015) 30(9):1193–9. PubMed PMID: 26072129; eng. doi:10.1007/s00384-015-2272-0

44. Kusters M, Beets GL, van de Velde CJ, Beets-Tan RGH, Marijnen CAM, Rutten HJT, et al. A comparison between the treatment of low rectal cancer in Japan and The Netherlands, focusing on the patterns of local recurrence. *Ann Surg* (2009) 249(2): 229–35. PubMed PMID: 19212175; eng. doi:10.1097/SLA.0b013e318190a664

45. Li B, Wu K, Li J, Wu Q, Wu Y, Wang X, et al. Locally advanced rectal mucinous adenocarcinoma: is preoperative radiation necessary? *J Gastrointest Oncol* (2022) 13(5): 2366–74. PubMed PMID: 36388693; PubMed Central PMCID: PMCPMC9660069. eng. doi:10.21037/jgo-22-817

46. Li WC, Zhao JK, Feng WQ, Miao YM, Xu ZF, Xu ZQ, et al. Retrospective research of neoadjuvant therapy on tumor-downstaging, post-operative complications, and prognosis in locally advanced rectal cancer. *World J Gastrointest Surg* (2021) 13(3): 267–78. PubMed PMID: 33796215; PubMed Central PMCID: PMCPMC7992997. eng. doi:10.4240/wjgs.v13.i3.267

47. Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma. Results of a prospective, randomized trial. *Dis Colon and Rectum* (1994) 37(12):1205–14. PubMed PMID: 7995145; eng. doi:10.1007/bf02257783

48. Oh SG, Park IJ, Seo JH, Kim YI, Lim SB, Kim CW, et al. Beware of early relapse in rectal cancer patients treated with preoperative chemoradiotherapy. *Ann Coloproctol* (2020) 36(6):382–9. PubMed PMID: 32674549; PubMed Central PMCID: PMCPMC7837400. eng. doi:10.3393/ac.2020.06.11

49. Peng HH, Zhou XH, Zhou TC, Qiu X, You K. Tumor location as an indication for adjuvant radiotherapy in pT3N0 rectal cancer after surgery. *Radiat Oncol (London, England)* (2019) 14(1):8. PubMed PMID: 30651116; PubMed Central PMCID: PMCPMC6334427. eng. doi:10.1186/s13014-019-1206-3

50. Spitale A, Franzetti-Pellanda A, Mazzola P, Richetti A, Mazzuchelli L, Bordoni A. Impact of preoperative radiotherapy on survival in locally advanced rectal cancer: an observational population-based study from the South of Switzerland. *Eur J Cancer Prev* (2012) 21(2):139–46. PubMed PMID: 22252302; eng. doi:10.1097/CEJ. 0b013e32834c9c56

51. Sun XY, Cai SH, Xu L, Luo D, Qiu H, Wu B, et al. Neoadjuvant chemoradiotherapy might provide survival benefit in patients with stage IIIb/IIIc locally advanced rectal cancer: a retrospective single-institution study with propensity score-matched comparative analysis. *Asia-Pacific J Clin Oncol* (2020) 16(3):142–9. PubMed PMID: 32031326; eng. doi:10.1111/ajco.13306

52. Sun Y, Lin H, Lu X, Huang Y, Xu Z, Huang S, et al. A nomogram to predict distant metastasis after neoadjuvant chemoradiotherapy and radical surgery in patients with locally advanced rectal cancer. *J Surg Oncol* (2017) 115(4):462–9. PubMed PMID: 28105657; eng. doi:10.1002/jso.24522

53. Wang F, Fan W, Peng J, Lu Z, Pan Z, Li L, et al. Total mesorectal excision with or without preoperative chemoradiotherapy for resectable mid/low rectal cancer: a long-term analysis of a prospective, single-center, randomized trial. *Cancer Commun (London, England)* (2018) 38(1):1–10. PubMed PMID: 30572939; PubMed Central PMCID: PMCPMC6302296. eng. doi:10.1186/s40880-018-0342-8

54. Yan H, Zhang Y, Hao Z, Lu Y, Liu H. mFOLFOX4 with or without radiation in neoadjuvant treatment of locally advanced middle and low rectal cancer. *J Cancer Res Ther* (2022) 18(7):2027–32. PubMed PMID: 36647966; eng. doi:10.4103/jcrt.jcrt_1207_22

55. Yeh CH, Chen MF, Lai CH, Huang WS, Lee SP, Chen WC. Comparison of treatment results between surgery alone, preoperative short-course radiotherapy, or long-course concurrent chemoradiotherapy in locally advanced rectal cancer. *Int J Clin Oncol* (2012) 17(5):482–90. PubMed PMID: 21938495; eng. doi:10.1007/s10147-011-0317-0

56. Yoon JE, Lee SY, Kwak HD, Yeom SS, Kim CH, Joo JK, et al. Oncologic outcomes of postoperative chemoradiotherapy versus chemotherapy alone in stage II and III upper rectal cancer. *Ann Coloproctol* (2019) 35(3):137–43. PubMed PMID: 31288502; PubMed Central PMCID: PMCPMC6625770. eng. doi:10.3393/ac.2018.09.28

57. Ma Z, Zhou J, Liu K, Chen S, Wu Q, Peng L, et al. Is radiotherapy necessary for upper rectal cancer underwent curative resection? A retrospective study of 363 patients. *Radiat Oncol (London, England)* (2024) 19(1):8. PubMed PMID: 38238776; PubMed Central PMCID: PMCPMC10797734. eng. doi:10.1186/s13014-024-02403-y

58. Duzova M, Basaran H, Inan G, Gul OV, Eren OO, Korez MK. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: outcomes of survival, toxicity, sphincter preserving and prognostic factors. *Transpl Immunol* (2021) 69:101489. PubMed PMID: 34687908; eng. doi:10.1016/j.trim.2021.101489

59. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a

median follow-up of 11 years. J Clin Oncol (2012) 30(16):1926–33. PubMed PMID: 22529255; eng. doi:10.1200/jco.2011.40.1836

60. Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. *Ann Surg* (2011) 253(4):711–9. PubMed PMID: 21475011; eng. doi:10.1097/SLA. 0b013e31820b8d52

61. Hale MF. Radiation enteritis: from diagnosis to management. *Curr Opin Gastroenterol* (2020) 36(3):208–14. PubMed PMID: 32141897; eng. doi:10.1097/mog. 00000000000632

62. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *The Lancet* (2009) 373(9666):821–8. PubMed PMID: 19269520; PubMed Central PMCID: PMCPMC2668948. eng. doi:10.1016/s0140-6736(09)60485-2

63. Bujko K, Nowacki MP, Oledzki J, Sopyło R, Skoczyłas J, Chwaliński M. Sphincter preservation after short-term preoperative radiotherapy for low rectal cancer-presentation of own data and a literature review. *Acta oncologica (Stockholm, Sweden)* (2001) 40(5):593–601. doi:10.1080/028418601750444132

64. Carlsen E, Schlichting E, Guldvog I, Johnson E, Heald RJ. Effect of the introduction of total mesorectal excision for the treatment of rectal cancer. *J Br Surg* (1998) 85(4):526–9. PubMed PMID: 9607540; eng. doi:10.1046/j.1365-2168. 1998.00601.x

65. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *J Br Surg* (2005) 92(2):211–6. PubMed PMID: 15584062; eng. doi:10.1002/bjs. 4806

66. Meng Z, Liu Z. Comparison of local excision and total mesorectal excision for rectal cancer: systematic review and meta-analysis of randomised controlled trial. *Heliyon* (2024) 10(9):e30027. PubMed PMID: 38720742; PubMed Central PMCID: PMCPMC11076819. eng. doi:10.1016/j.heliyon.2024.e30027

67. Mulita F, Liolis E, Akinosoglou K, Tchabashvili L, Maroulis I, Kaplanis C, et al. Postoperative sepsis after colorectal surgery: a prospective single-center observational study and review of the literature. *Gastroenterol Rev* (2022) 17(1):47–51. PubMed PMID: 35371356; PubMed Central PMCID: PMCPMC8942007. eng. doi:10.5114/pg. 2021.106083

68. Verras GI, Mulita F. Butyrylcholinesterase levels correlate with surgical site infection risk and severity after colorectal surgery: a prospective single-center study.

Front Surg (2024) 11:1379410. PubMed PMID: 39229253; PubMed Central PMCID: PMCPMC11368738. eng. doi:10.3389/fsurg.2024.1379410

69. Kehagias D, Lampropoulos C, Bellou A, Kehagias I. The use of indocyanine green for lateral lymph node dissection in rectal cancer-preliminary data from an emerging procedure: a systematic review of the literature. *Tech Coloproctol* (2024) 28(1):53. PubMed PMID: 38761271; PubMed Central PMCID: PMCPMC11102372. eng. doi:10. 1007/s10151-024-02930-6

70. Bousis D, Verras GI, Bouchagier K, Antzoulas A, Panagiotopoulos I, Katinioti A, et al. The role of deep learning in diagnosing colorectal cancer. *Gastroenterol Rev* (2023) 18(3):266–73. PubMed PMID: 37937113; PubMed Central PMCID: PMCPMC10626379. eng. doi:10.5114/pg.2023.129494

71. Chlorogiannis DD, Verras GI, Tzelepi V, Chlorogiannis A, Apostolos A, Kotis K, et al. Tissue classification and diagnosis of colorectal cancer histopathology images using deep learning algorithms. *Gastroenterol Rev* (2023) 18(4):353–67. PubMed PMID: 38572457; PubMed Central PMCID: PMCPMC10985751. eng. doi:10.5114/pg.2023. 130337

72. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* (2006) 93(10):1215–23. PubMed PMID: 16983741; eng. doi:10.1002/bjs.5506

73. Latkauskas T, Pauzas H, Gineikiene I, Janciauskiene R, Juozaityte E, Saladzinskas Z, et al. Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery. *Colorectal Dis* (2012) 14(3):294–8. PubMed PMID: 21899712; eng. doi:10.1111/j.1463-1318.2011. 02815.x

74. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet (London, England)* (2001) 358(9290):1291–304. PubMed PMID: 11684209; eng. doi:10.1016/s0140-6736(01)06409-1

75. Cammà C, Giunta M, Fiorica F, Pagliaro L, Craxì A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: a meta-analysis. *Jama* (2000) 284(8):1008–15. PubMed PMID: 10944647; eng. doi:10.1001/jama.284.8.1008

76. Wang X, Han Y, Zhi Z, Xu W, Ge J, Liang X, et al. Delineation of the "oropharyngeal mucosa" and limiting its dose in head and neck cancer patients spares the oropharynx without compromising target coverage. *Cancer Control* (2024) 31:10732748241283621. doi:10.1177/10732748241283621