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Review Article

Optimal surgical timing following neoadjuvant chemoradiotherapy in patients with rectal cancer: a systematic review and network meta-analysis

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Abstract: Objective: To determine the optimal surgical interval between neoadjuvant chemoradiotherapy (nCRT) and total mesorectal excision (TME) for patients with locally advanced rectal cancer through a network meta-analysis (NMA). Additionally, a continuous dose-response meta-regression analysis was conducted to explore potential non-linear associations. Methods: Electronic databases, including PubMed, Embase, Web of Science, and the Cochrane Library, were systematically searched from inception to July 18, 2024. The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2.0 (ROB 2.0) tool and the Newcastle-Ottawa Scale (NOS). The NMA was performed under a Bayesian framework, and surgical intervals ranging from <4 weeks to 28 weeks were ranked using the surface under the cumulative ranking curve (SUCRA). The primary endpoint was pathological complete response (pCR), while secondary endpoints included overall survival (OS), disease-free survival (DFS), recurrence rate, and sphincter preservation rate (SPR). Results: A total of 12 studies (3 randomized controlled trials and 9 cohort studies) involving 31,783 patients were included. SUCRA rankings indicated that an interval of 8-12 weeks was most effective for achieving pCR, prolonging DFS, and reducing recurrence rate. Conversely, a 6-8 week interval was most favorable for improving OS and SPR. Both very short (<4 weeks) and very long (>24 weeks) intervals ranked lower across most clinical outcomes. Dose-response analysis revealed a significant inverted U-shaped association for pCR, mathematically peaking at approximately 12.7 weeks, whereas DFS showed a peak at around 5.9 weeks. Conclusion: Current evidence suggests that an interval of 8-12 week is most strongly associated with improved pCR and prolonged DFS, whereas a 6-8 week interval shows the highest probability of improving OS and SPR. Clinical decision-making should balance oncologic and functional outcomes based on individualized assessments.

Keywords: Rectal cancer, neoadjuvant chemoradiotherapy, surgical interval, network meta-analysis, pathological complete response

Introduction

Colorectal cancer (CRC) is one of the most common malignancies and poses a substantial global health burden. According to the Cancer Statistics 2022, CRC ranks third in incidence and second in cancer-related mortality worldwide [1]. In recent years, its epidemiological pattern has evolved: while the incidence in population aged >50 years has declined by approximately 2% per year, it has increased by approximately 1.5% per year in young populations, indicating a rising tendency in early-onset CRC [1]. Owing to the insidious onset of symptoms, more than 70% of patients are diagnosed at an advanced stage [2], and the 5-year survival rate of patients remains significantly lower than that of early-stage patients.

In this clinical setting, neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) is now considered the standard treatment paradigm for locally advanced RC [3, 4]. The primary objectives of this approach are to downstage the tumor and reduce tumor volume, increasing the likelihood of achieving radical (R0) resection, improving loco-regional control, and enhancing the probability of sphincter preservation, ultimately contributing to survival outcomes [3, 5-7]. In particular, for patients

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with stage II/III disease, preoperative nCRT has been shown to reduce the risk of locoregional recurrence [8].

Despite its widespread adoption, the optimal interval between completion of nCRT and subsequent TME remains unclear. Existing evidence is limited and conflicting. Early studies (Lyons R90-01 trial) suggested that a 6-8 week interval significantly improves tumor downstaging, supporting a moderate delay before surgery [9]. Subsequent observational studies proposed that prolonging the duration to 9-12 weeks might further increase the pathological complete response (pCR) rate without increasing surgical complications or compromising overall survival (OS) [10]. However, contradictory findings have also been reported. For example, in the GRECCAR-6 study, an 11-week interval didn't improve pCR rates but was associated with increased operative complexity and post-operative complications [11]. In addition, some studies have indicated that excessively prolonged intervals (>12 weeks) might adversely affect OS in patients without pCR [12] or be correlate to lower rates of sphincter preservation [13, 14]. While certain studies suggest potential survival benefits with longer intervals (9-14 weeks) [15], others have reported no additional advantage beyond 12 weeks in terms of tumor regressions or survival outcomes [16].

Given these conflicting results, the time of surgery after nCRT remains one of the most controversial issues in clinical decision-making. Hence, this study aims to perform a network meta-analysis (NMA) to systematically compare the effects of different surgical intervals (<4 weeks, 8-12 weeks, 16-20 weeks, and 20-24 weeks) across multiple clinically relevant outcomes, including pCR, OS, disease-free survival (DFS), recurrence rate, and sphincter preservation rate (SPR). By providing quantitative comparative evidence, this study seeks to facilitating more informed and individualized determination of the optimal time interval (OTI) for surgery.

Methods

This study was registered in PROSPERO (CRD42024576939) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17].

Search strategy

Electronic databases, including PubMed, Embase, Web of Science, and the Cochrane Library, were searched from inception to July 18, 2024. The search strategy combined controlled vocabulary (e.g., MeSH terms) and free-text terms. Search terms included "rectal neoplasms", "rectum tumor", "neoadjuvant therapy", "neoadjuvant therapy", "surgical procedures", "operative", "surgery", and "interval". The detailed search strategy is summarized in Table S1.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients aged ≥18 years with locally advanced RC who underwent TME after nCRT; (2) studies comparing the prognostic impacts of different intervals between nCRT and surgery; (3) cohort studies or randomized controlled trials (RCTs); (4) publications in English. In this study, the primary outcome measure was pCR, and secondary outcome measures included OS, DFS, the recurrence rate, and SPR.

Exclusion criteria : (1) non-original studies, including editorials, reviews, and meta-analyses; (2) studies involving patients with advanced RC who did not receive both nCRT and surgical resection; or (3) ongoing clinical trials.

All reported intervals were extracted as defined in each study and categorized a priori into the following groups: <4, 4-6, 6-8, 8-12, 12-16, 16-20, 20-24, and 24-28 weeks. Although the 24-28 week interval was reported in only one study [16], it was retained in the network meta-analysis to ensure a comprehensive evaluation of extended surgical delays and to maximize the use of available clinical evidence.

Literature screening

Two investigators (Zijie Tao and Qiyi Gui) separately screened the literature using EndNote X9 according to the predefined inclusion and exclusion criteria. Titles and abstracts reviewed first, followed by full-text assessment of potentially eligible studies. Information extracted from the included studies comprised the first author, year of publication, sample size, age, time interval to surgery, nCRT regimen, type of surgery, outcome measures, and other relevant information. Any discrepancies arising during litera-

ture screening or data extraction were resolved through discussion with a third investigator (Yuhang Jiang). All extracted data were subsequently double-checked to ensure accuracy.

Quality assessment

RCTs were assessed based on version 2 of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) [18]. Each study was classified as having "low risk", "high risk", or "some concerns". Discrepancies in quality assessment were resolved via discussion with a third investigator. The risk of bias was evaluated across five domains: (1) bias from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in outcome measurement, and (5) bias in selection of the reported result.

Cohort studies included in the NMA were subjected to quality assessment using the Newcastle Ottawa Scale (NOS) [19], which encompassed eight items: (1) representativeness of the exposed cohort, (2) selection of the non-exposed cohort, (3) ascertainment of exposure, (4) confirmation that the outcome of interest was not present at baseline, (5) comparability of cohorts based on study design or analysis, (6) outcome assessment, (7) adequacy of follow-up duration, and (8) completeness of cohort follow-up.

Of the eight items, the comparability domain was assigned a maximum of 2 points, while each of the remaining was assigned a maximum of 1 point, resulting in a total score of 9 points. Study quality was categorized as high (7-9 points), moderate (4-6 points), and low (0-3 points).

Statistical analysis

The network meta-analysis (NMA) was conducted within a Bayesian framework utilizing Markov Chain Monte Carlo (MCMC) simulation to compare the efficacy of various surgical intervals across clinical outcomes. For each endpoint, model convergence was assessed using four independent Markov chains with 50,000 iterations following a burn-in period of 20,000 iteration. Convergence was confirmed by a potential scale reduction factor (PSRF) approximating 1.0. Inter-study heterogeneity was rigorously assessed using the I^2 statistic and Cochran's Q test. Significant heterogeneity (defined as $I^2>50\%$ or $P<0.10$ for the Q test) prompted the adoption of a random-effects model, whereas a fixed-effects model was employed. To ensure the robustness of the network, the node-splitting method was applied to evaluate the consistency between direct and indirect evidence, with $P>0.05$ denoting no significant inconsistency. Effect estimates were expressed as relative risks (RR) with corresponding 95% credible intervals (CrI). The ranking probability of each surgical interval for pCR, OS, DFS, SPR, and recurrence rates was determined using the surface under the cumulative ranking curve (SUCRA), with higher values signifying better performance. Publication bias and small-study effects were evaluated using funnel plots and Egger's regression test, with $P<0.05$ considered significant. All computational procedures were performed using R software (version 4.2.0) utilizing the "gemtc" and "rjags" packages.

Dose-response meta-analysis

To further evaluate the continuous relationship between the surgical interval and clinical outcomes, a study-level dose-response meta-regression analysis was performed. Categorical interval groups were converted into a continuous exposure variable (in weeks) by assigning the midpoint of each defined range (e.g., the 6-8 week interval was assigned a value of 7 weeks). For open-ended intervals (e.g., <4 weeks), clinically plausible values were assigned. A weighted least squares (WLS) regression model with study-level cluster-robust standard errors was fitted. To capture potential nonlinear associations, both linear and quadratic terms were included into the model to predict the empirical log-odds of each outcome. For outcomes with statistically significant quadratic terms, the turning points (i.e., peaks) of the fitted curves were calculated.

Results

Search results

A total of 9,025 studies were initially retrieved based on the predefined search strategy. After removal of duplicates, 64 studies remained for screening. After title and abstract screening according to the inclusion and exclusion criteria, full-text assessments were conducted for

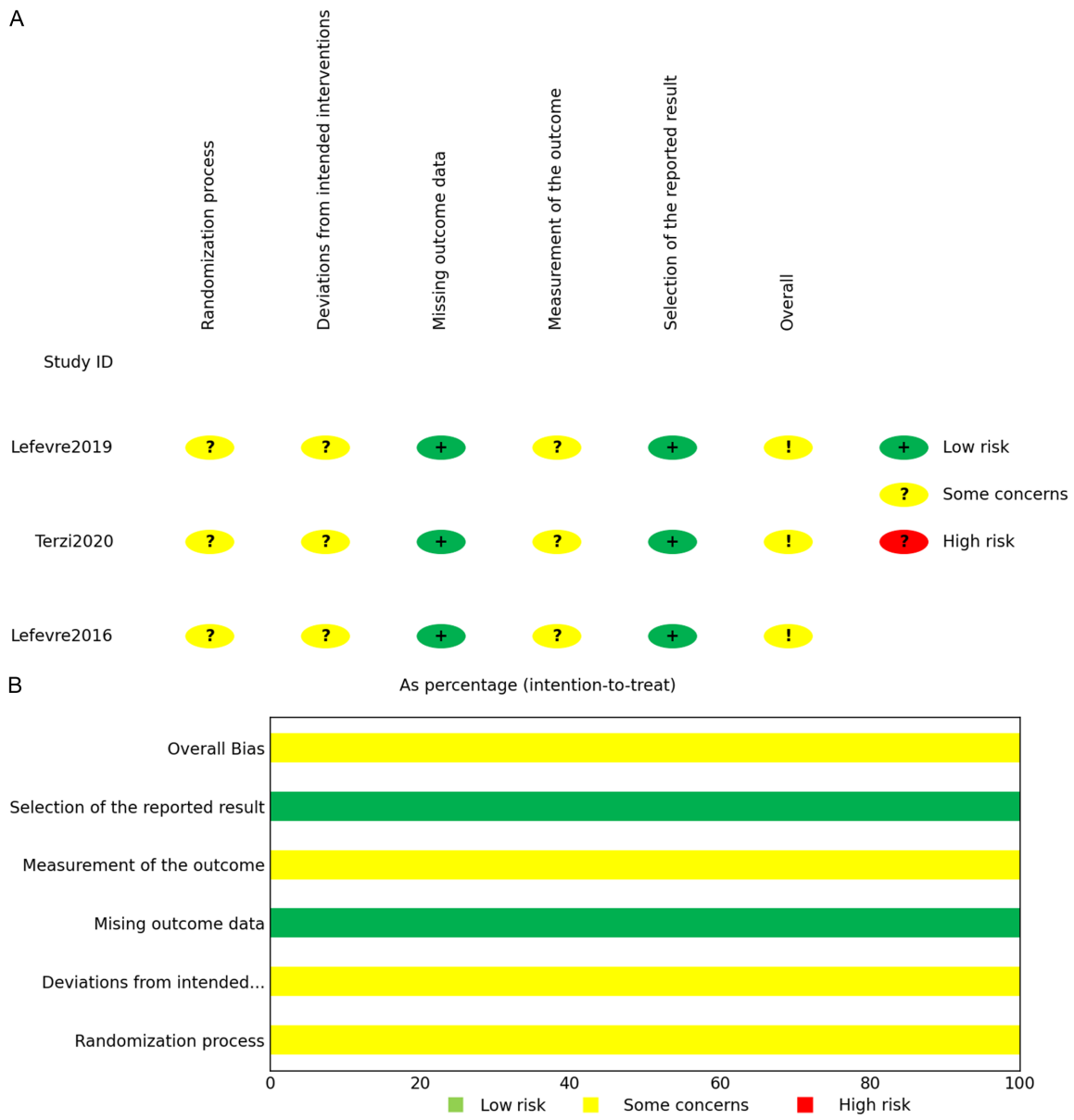

Figure 1. Risk of bias (RoB) graph and a summary of the included studies: (A) Reviewers' judgments about each RoB item for eligible studies and (B) Judgments about each RoB item presented as percentages across all eligible studies.

all 64 studies. Of them, 29 studies were excluded due to unavailable or insufficient data for extraction, 22 were excluded because the interventions did not meet the inclusion criteria, and 1 was excluded due to the absence of relevant outcome measures. Finally, 12 studies were included in this study, comprising a total of 31,783 patients (**Figure 2**). Quality assessment based on the NOS is summarized in **Table 2**, indicating that most included studies were of high methodological quality.

Characteristics of the included studies

Of the 12 included studies, 9 were cohort studies while 3 were RCTS, encompassing a total of 31,783 patients. The mean age ranged from 43.46 to 65.21 years, and publication years spanned from 2013 to 2024.

Regarding surgical intervals, 1 study reported an interval of ≤4 weeks, 2 studies reported 4-6 weeks, 9 studies reported 6-8 weeks, 11 studies reported 8-12 weeks, 5 studies reported

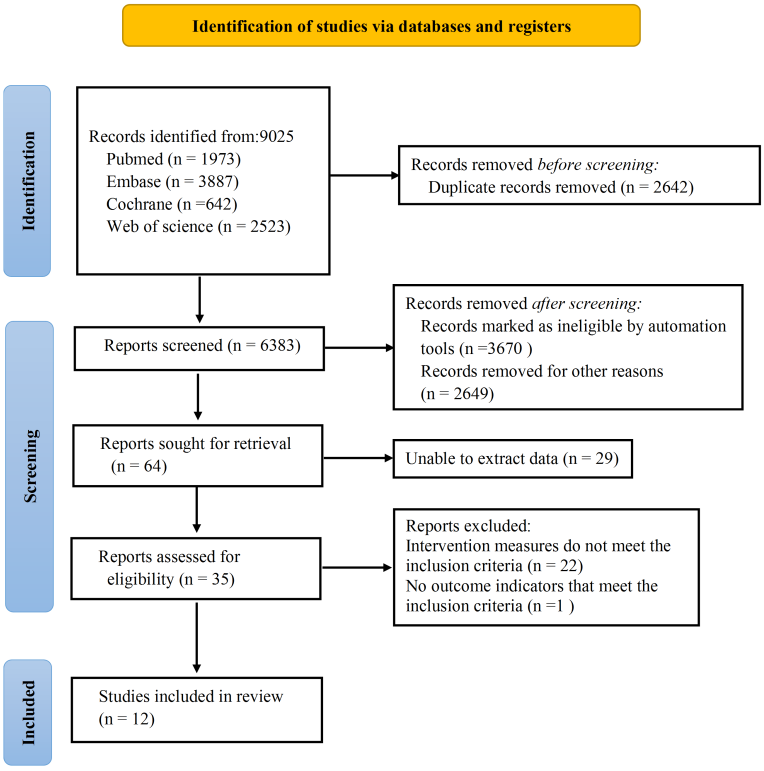

Figure 2. Flowchart of study search and selection.

12-16 weeks, 1 study reported 16-20 weeks, and 1 study reported 20-24 weeks. Among these reports, one study reported an interval of 24-28 weeks. In terms of outcome measurements, 9 studies reported pCR, 3 reported OS, 4 reported DFS, 6 reported recurrence rate, and 4 reported SPR. The detailed characteristics of all included studies are summarized in **Table 1**.

Results of quality assessment

According to ROB 2 tool, 3 studies were assessed as having moderate risk (**Figure 1**). According to the NOS, 1 study was rated as moderate quality (4-6 points), and 8 studies were rated as high quality (7-9 points), as detailed in Table S2.

pCR

A total of nine studies [10, 12, 20-26], encompassing 31,317 patients, were incorporated into the analysis of pCR. The network structure is shown in **Figure 3A**.

The league table (**Figure 4A**) showed that, compared with an interval of <4 weeks, significantly higher pCR rates were observed for intervals of 6-8 weeks (RR: 1.65; 95% CrI: 1.23-2.2), 8-12 weeks (RR: 1.99; 95% CrI: 1.62-2.48), 12-16 weeks (RR: 1.79; 95% CrI: 1.43-2.27), 16-20 weeks (RR: 1.69; 95% CrI: 1.26-2.25), and 20-24 weeks (RR: 1.63; 95% CrI: 1.13-2.33).

The SUCRA ranking results showed that the 8-12 week interval had highest probability of achieving pCR (96.5%), followed by 12-16 weeks (68.7%), and 16-20 weeks (55.9%) (**Figure 5A**).

Secondary outcomes

OS: Three studies [16, 20, 26], involving 401 patients, were included in the analysis of OS. The network structure is shown in **Figure 3B**.

The league table (**Figure 4B**) showed that, with 4-6 weeks as the reference group, significantly higher OS was observed for the 6-8-week interval (HR: 1.25; 95% CI: 1.02-1.58) and the 8-12-week interval (HR: 1.19; 95% CI: 1.01-1.44), indicating that both longer intervals were associated with better OS compared with 4-6 weeks. The 24-28-week interval showed a numerically lower OS compared with 4-6 weeks (HR: 0.41; 95% CI: 0.12-1.05), though this did not reach statistical significance, likely due to the small sample size of that subgroup. The SUCRA results showed that the 6-8 week interval had the highest probability of being optimal for OS (91.6%), followed by 8-12 weeks (73.3%) and 4-6 weeks (33.3%) (**Figure 5D**).

DFS: Four studies [11, 16, 20, 26], including 654 patients, were included in the DFS analysis. The network structure is shown in **Figure 3C**.

The league table (**Figure 4C**) demonstrated that compared with the 4-6-week interval, the 6-8-week interval (RR: 0.65; 95% CrI: 0.46-0.90) and 8-12-week interval (RR: 0.65; 95% CrI: 0.47-0.86) were associated with higher DFS.

Table 1. Baseline characteristics of included studies

Study (year)	Sample Size	Time interval (weeks)	Neoadjuvant therapy	Type of surgery	Follow-up (months)	cTNM Stage	Outcome	Quality assessment
Kammar [16] 2020	161	6-8, 8-12, 24-28	Capecitabine + 50.4 Gy	TME	Median: 49.5 (range: 4-69)	T3-4: 87.5%; Node positive: 83.2%	OS, DFS, recurrence rate, SPR	Low risk
Mihmanlı [26] 2016	87	4-6, 8-12	5-fluorouracil + 45-50.4 Gy (5 × 1.8-2.0 Gy/week)	TME	Median: 34.5 (9.9-81)	Stage III: 89.7%; T3-4: 83.9%	pCR, OS, DFS, recurrence rate	Low risk
Jeong [20] 2013	153	6-8, 8-12	45 Gy (1.8 Gy/fraction)	TME	Median: 47 (7-108)	T3-4: 92.2%; cN+: 79.7%	pCR, OS, DFS, recurrence rate	Low risk
Sirohi [21] 2014	110	6-8, 8-12	5-fluorouracil (425 mg/m^2/day) + folic acid (20 mg/m^2/day)	Surgery	Median: 24 (6-54)	T3-4: 100%; cN+: 80.0%	pCR, recurrence rate, SPR	Low risk
Rombouts [10] 2016	1073	4-6, 6-8, 8-12, 12-16	5-fluorouracil + 45-50 Gy (1.8-2 Gy/fraction)	Surgery	NR	T3-4: 81.1%; cN+: 76.4%	pCR	Low risk
Terzi [23] 2020	252	8-12, 12-16	Capecitabine (825 mg/m^2, twice daily, 5 days a week) and 5-fluorouracil (225 mg/m^2 daily) + 45 Gy (1.8 Gy/fraction)	TME	Median: 25.4 (6-57)	T3-4: 95.2%; cN+: 84.5%	pCR, SPR	Some concerns
Lefèvre [11] 2019	253	6-8, 8-12	5-fluorouracil/capecitabine +45-50 Gy	TME	Median: 46.4	T3-4: 100%; cN+: 84.6%	DFS, recurrence rate	Some concerns
Piva [22] 2022	114	6-8, 8-12	5-fluorouracil/capecitabine + 50.4 Gy	TME	Median: 42 (6-133)	T3-4: 89.5%; cN+: 84.2%	pCR	Low risk
Amin [12] 2024	28656	<4, 8-12, 12-16, 16-20, 20-24	50 Gy/25 fractions/ 50.4 Gy/28 fractions/ 50 Gy/30 fractions	Surgery	Median: 64.9 (1.0-175.0)	T3-4: 85.4%; cN+: 69.4%	pCR	Low risk
Garrer [15] 2016	52	6-8, 8-12	Xeloda (825 mg/m^2, twice daily) + 45 Gy/25 fractions/5 weeks + 5.4 Gy/3 fractions (enhanced radiation therapy against tumors)	TME	Mean: 24.1 (6.1-61.5)	T3-4: 100%; cN+: 75.0%	Recurrence rate	Some concerns
Roxburgh [24] 2019	607	6-8, 8-12, 12-16	Fluorouracil combined with oxaliplatin/long-course radiotherapy, with fluorouracil or capecitabine/combination of fluorouracil and oxaliplatin	TME	Median: 45 (24.4-73.2)	T3-4: 92.5%; cN+: 85.8%	pCR	Low risk
Lefevre [25] 2016	265	6-8, 8-12	Capecitabine/fluorouracil + 45-50 Gy	TME	Median: 20.6 (12.5-29.2)	T3-4: 100%; cN+: 84.2%	pCR, SPR	Some concerns

Note: nCRT, neoadjuvant chemoradiotherapy; TME, total mesorectal excision; pCR, pathologic complete response; OS, overall survival; DFS, disease-free survival; SPR, sphincter preservation rate; cTNM, clinical tumor-node-metastasis; NR, not reported.

Table 2. Quality assessment of all included studies based on NOS (Newcastle-Ottawa Scale)

Study (Year)	Selection (Max 4★)	Comparability (Max 2★)	Outcome (Max 3★)
Amin 2024	★★★★	★★	★★★
Rombouts 2016	★★★★	★★	★★★
Lefevre 2019 (RCT)	★★★★	★★	★★★
Terzi 2020 (RCT)	★★★★	★★	★★★
Roxburgh 2019	★★★★	★★	★★★
Lefevre 2016 (RCT)	★★★★	★★	★★★
Jeong 2013	★★★	★★	★★★
Mihmanlı 2016	★★★	★★	★★
Kammar 2020	★★★	★	★★
Piva 2022	★★★	★	★★
Garrer 2016	★★★	★	★★
Sirohi 2014	★★★	★	★★

The SUCRA results showed that 8-12 weeks ranked first (84.0%), 6-8 weeks ranked second (82.5%), and 4-6 weeks ranked third (33.4%) (**Figure 5C**).

Recurrence rate: Six studies [11, 15, 16, 20, 21, 26], involving 816 patients, were included in the analysis of recurrence rate. The network structure is illustrated in **Figure 3D**. The league table (**Figure 4D**) showed that, with 4-6 weeks as the reference group, no significant differences in recurrence rates were observed among the various surgical interval groups, although the 8-12-week interval exhibited the most favorable point estimate for recurrence reduction.

The SUCRA results showed that 8-12 weeks ranked first (68.8%), 24-28 weeks ranked second (46.3%), and 6-8 weeks ranked third (43.8%), as shown in **Figure 5B**.

Sphincter preservation rate: Four studies [16, 21, 23, 25], including 776 patients, were included in the analysis of SPR. The network structure is shown in **Figure 3E**.

The league table (**Figure 4E**) showed that, compared with the 6-8 week interval, significantly lower SPR was observed for the 12-16 week interval (RR: 0.85; 95% CrI: 0.73-0.98) and 24-28 week interval (RR: 0.59; 95% CrI: 0.40-0.83).

SUCRA results showed that the 6-8 week interval had the highest probability of being optimal for SPR (89.1%), followed by 8-12 weeks (76.8%) and 12-16 weeks (33.2%) (**Figure 5E**).

It should be noted that while 6-8 weeks ranked first in probability, the direct comparison between the 6-8 weeks and 8-12 weeks groups showed no significant difference (RR=0.98, 95% CrI 0.90-1.06; **Figure 4E**). Therefore, 6-8 weeks is considered the most probable favorable window rather than an absolute optimal choice.

Dose-response meta-analysis

To further explore the continuous relationship between surgical intervals and clinical outcomes, a dose-response meta-regression was performed. A significant non-linear (inverted U-shaped) association was identified for pCR ($P<0.001$ for the quadratic term) and DFS ($P=0.037$). The fitted curves demonstrated that the probability of achieving pCR increases with longer intervals but reached a mathematical peak at approximately 12.7 weeks, while DFS peaked at around 5.9 weeks. However, these peaks should be interpreted as statistical trend rather than definitive clinical threshold, as they may be influenced by the relatively sparse data in shorter intervals (e.g., 4-6 weeks) compared with the more data-rich 8-12 week interval. No significant response relationships were observed for OS, recurrence rate, or SPR (**Figure 6**).

Consistency and publication bias

Model consistency and convergence were rigorously evaluated to ensure the validity of the network estimates. The node-splitting method was used to assess agreement between direct and indirect evidence. As shown in **Table 3**, all node-split *P*-values exceeded 0.05 (e.g., pCR: P=0.428; DFS: P=0.612), demonstrating no significant local inconsistency and supporting the reliability of the pooled estimates.

Additionally, model convergence was confirmed by potential scale reduction factor (PSRF) approaching 1.0 across all parameters, indicating adequate convergence of the Bayesian MCMC chains. Publication bias was assessed using comparison-adjusted funnel plots for

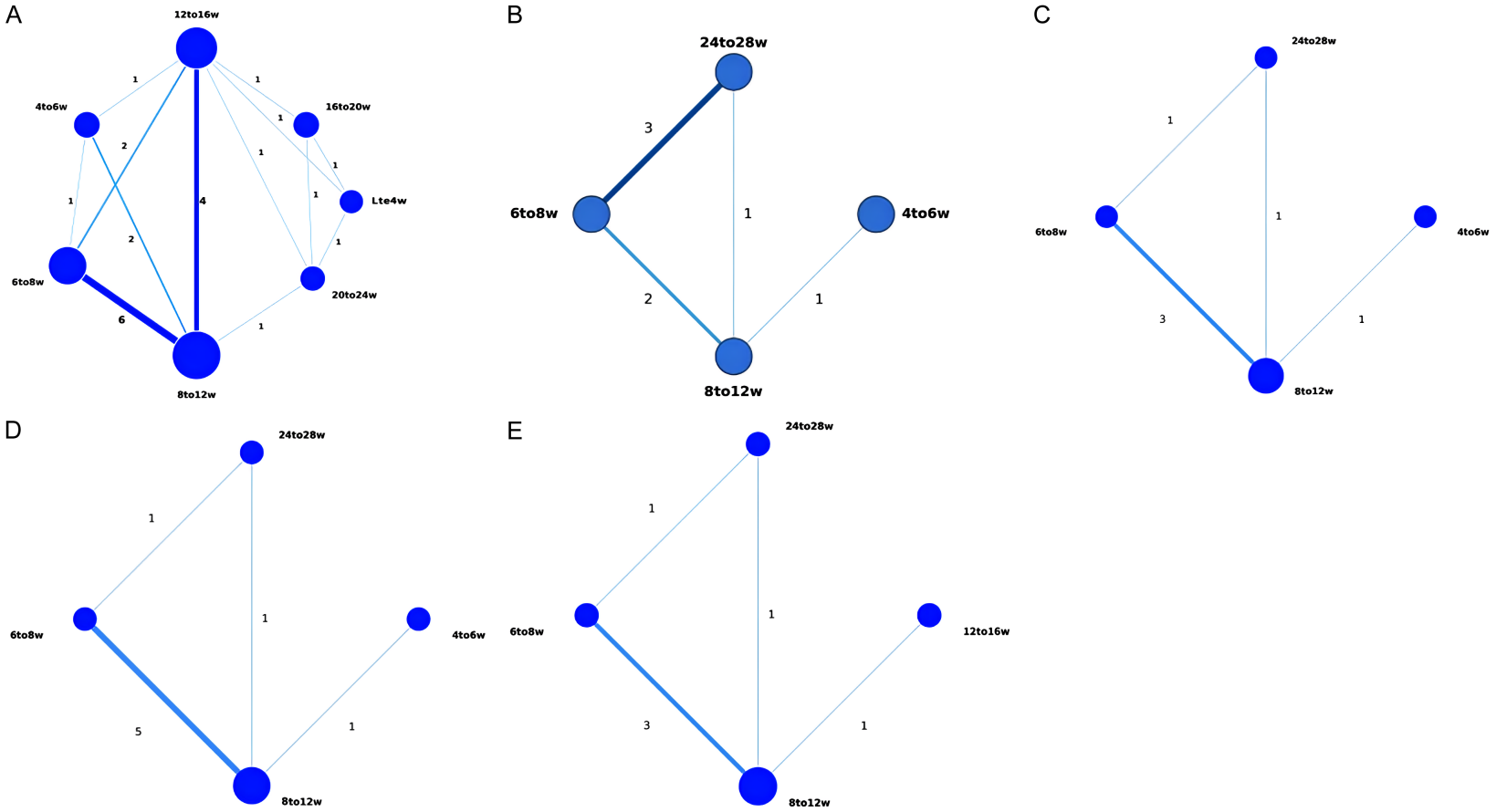

Figure 3. Network diagram of different outcome indicators. (A) pCR (Pathologic Complete Response); (B) OS (Overall Survival); (C) DFS (Disease-Free Survival); (D) Recurrence Rate; (E) SPR (Sphincter Preservation Rate). The size of each node is proportional to the number of patients for that interval. The width of the lines connecting nodes is proportional to the number of studies making that direct comparison.

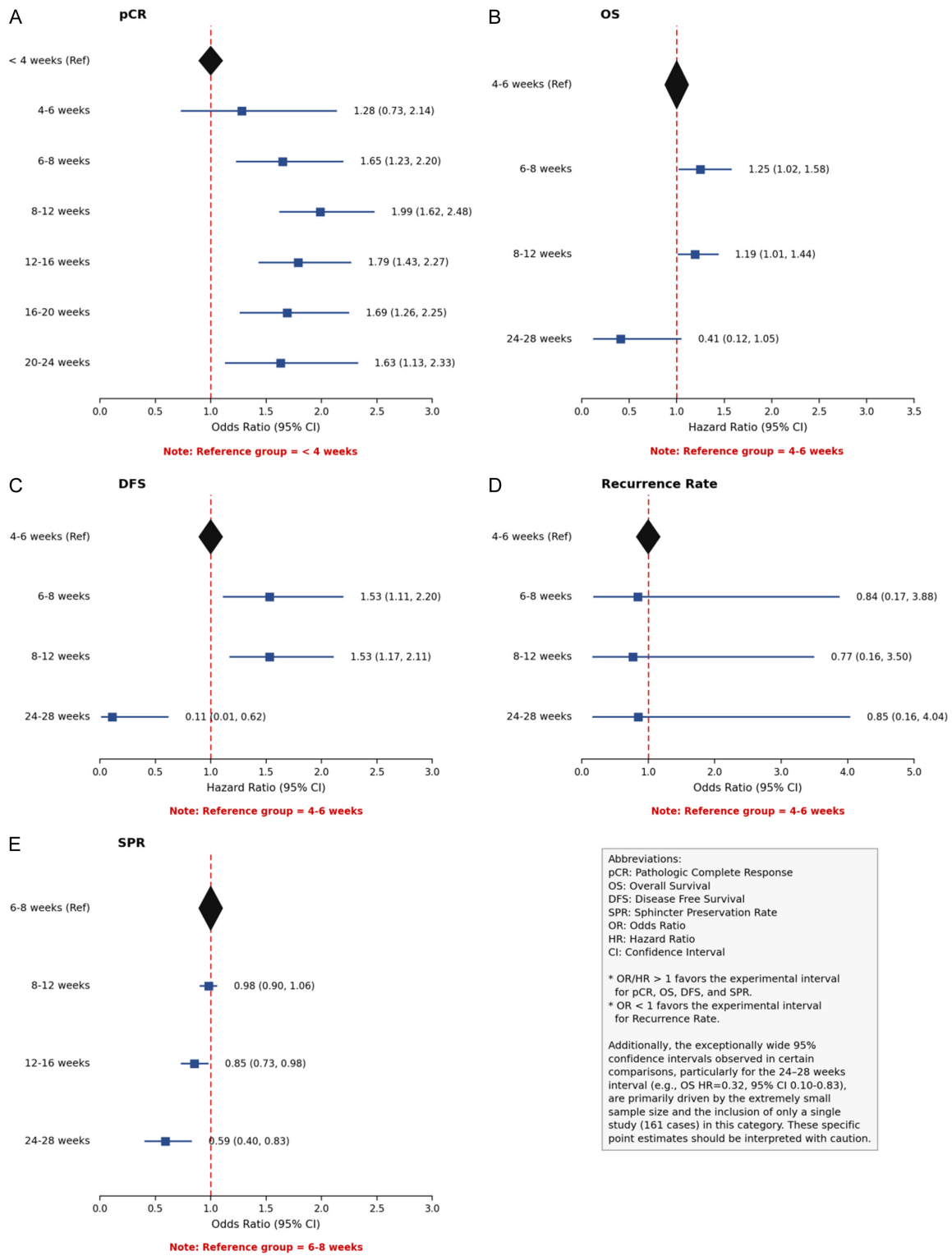

Figure 4. Forest plots of network meta-analysis for all clinical outcomes. A. pCR (Pathologic Complete Response); B. OS (Overall Survival); C. DFS (Disease Free Survival); D. Recurrence Rate; E. SPR (Sphincter Preservation Rate). Note: The <4 weeks group was used as the reference group for pCR; the 4-6 weeks group was used as the reference group for OS, DFS, and recurrence rate; and the 6-8 weeks group was used as the reference group for SPR. Results are presented as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals(CIs).

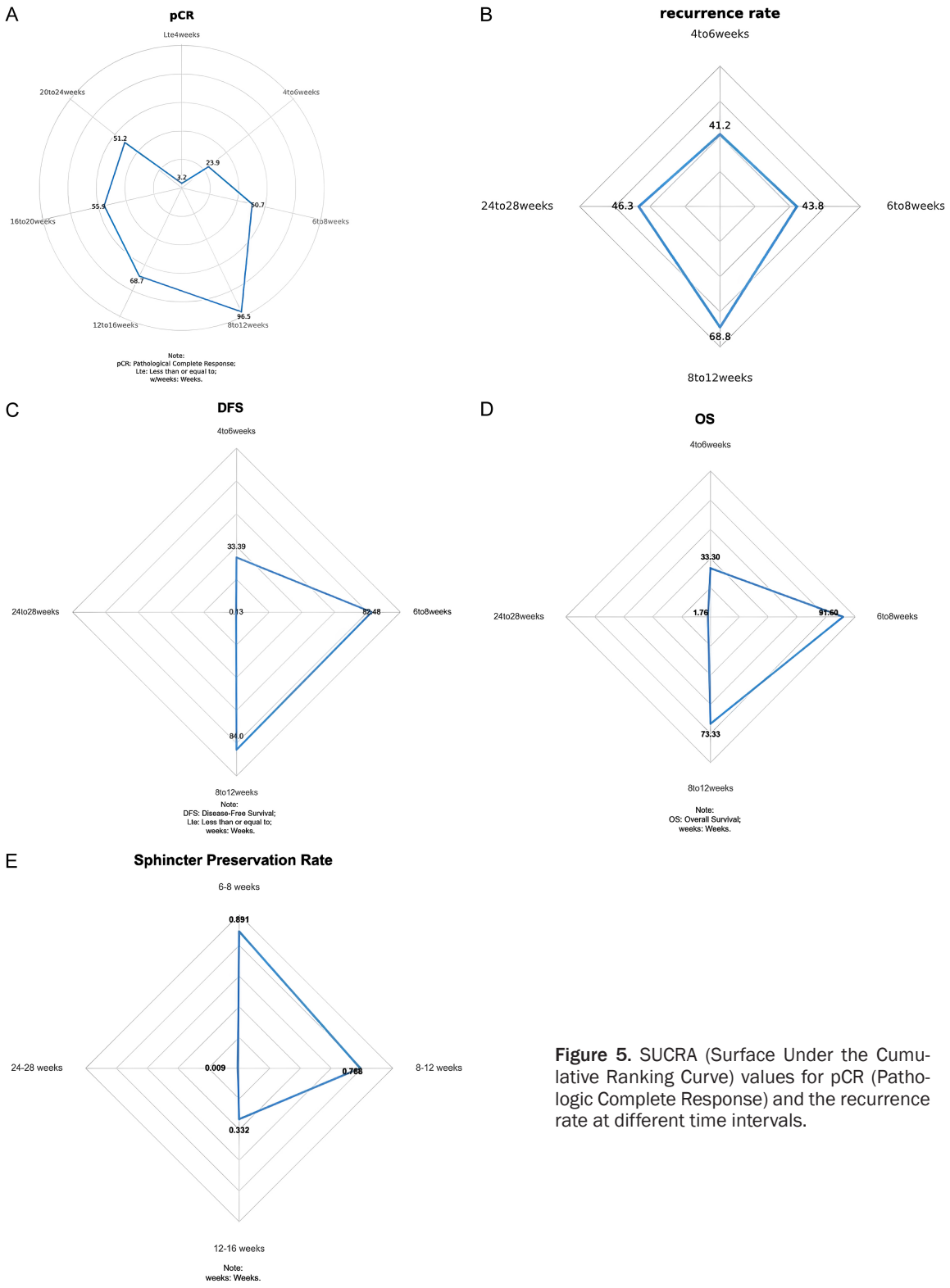

Figure 5. SUCRA (Surface Under the Cumulative Ranking Curve) values for pCR (Pathologic Complete Response) and the recurrence rate at different time intervals.

the primary outcome (pCR). Visual inspection revealed a generally symmetrical distribution of studies around the null line, indicating a minimal risk of publication bias across the network. This was further corroborated by Egger's regression test (P=0.456), suggesting that small-study effects did not significantly influence the overall clinical conclusions (**Figure 7**).

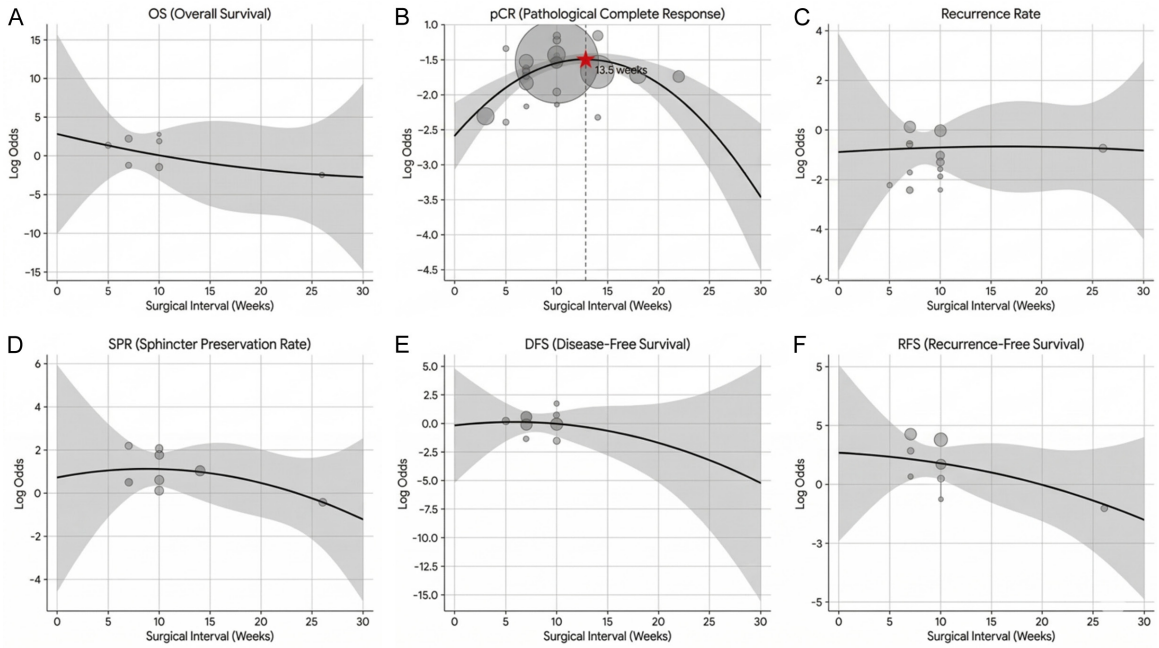

Figure 6. Dose-response meta-regression curves for clinical outcomes. The solid lines represent the fitted quadratic trends, illustrating an inverted U-shaped relationship for pCR (Pathologic Complete Response) and DFS (Disease-Free Survival). The shaded areas surrounding the solid lines represent the 95% confidence bands, providing a visual measure of the reliability and precision of the curve trends. Points represent the empirical log-odds from individual study arms.

Table 3. Summary of SUCRA (Surface Under the Cumulative Ranking Curve) rankings for all clinical outcomes

Outcome Measure	Best Interval (SUCRA %)	Second Best (SUCRA %)	Consistency *P*-value*
pCR	8-12 weeks (96.5%)	12-16 weeks (68.7%)	>0.05
OS (Overall Survival)	6-8 weeks (91.6%)	8-12 weeks (73.3%)	>0.05
DFS (Disease-Free Survival)	8-12 weeks (84.0%)	6-8 weeks (82.5%)	>0.05
Anal Preservation Rate	6-8 weeks (89.1%)	8-12 weeks (76.8%)	>0.05
Recurrence Rate	8-12 weeks (68.8%)	24-28 weeks (46.3%)	>0.05

Note: SUCRA, surface under the cumulative ranking curve; pCR, pathologic complete response; OS, overall survival; DFS, disease-free survival. Consistency *P*-value derived from the node-splitting method; *P>0.05 indicates no significant inconsistency between direct and indirect evidence.

Discussion

The optimal timing of surgery following completion of nCRT remains one of the major unresolved issues in the management of locally advanced rectal cancer (LARC). In this study, we conducted a comprehensive NMA including 31,783 patients to comprehensively evaluate the impact of various interval windows across a set of competing clinical outcomes. Our findings suggest that the optimal interval is not uniform across endpoints. Specifically, an interval of 8-12 weeks appears to be most favorable for achieving pCR and DFS, whereas a shorter interval of 6-8 weeks may be more beneficial for OS and SPR. These results highlight the inherent trade-off between oncologic and functional outcomes, underscoring the need for individualized decision-making in clinical practice.

With regard to tumor response and DFS, the superiority of the 8-12 week interval is biologically reasonable. This frame allows for continued tumor regression driven by chemotherapy- and irradiation-induced apoptosis and immune-mediated tumor clearance. Evidence suggests that the tumor immune microenviron-

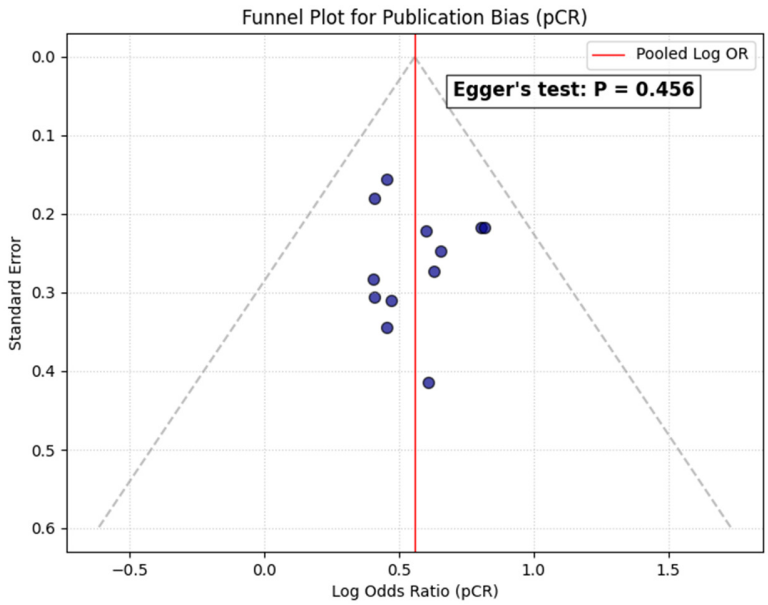

Figure 7. Funnel plot for the assessment of publication bias. The funnel plot illustrates the relationship between study precision and effect size for the primary outcome, pCR (Pathologic Complete Response). The visual symmetry of the plot, combined with the result of Egger's test (P=0.456), indicates no significant evidence of publication bias within the network.

ment evolves dynamically following nCRT, with delayed intervals potentially enhancing antitumor immune activity [8, 24, 26-28], which is consistent with the obviation of lower recurrence rate within this interval in our study. However, there seems to exist an eventual maximum time limit to this waiting period. Beyond approximately 12 weeks, the risk for residual clonal proliferation may offset the advantages of delayed surgery, indicating the existence of a biologically critical window.

Regarding survival outcomes, our finding that the 8-12 week interval optimizes DFS is consistent with previous meta-analysis by Sun et al. [14], although it differs from some RCTs that reported no significant survival difference. This discrepancy may stem from the fact that while local response (pCR) is time-dependent, long-term DFS is more influenced by systemic micrometastases. From a clinical perspective, a moderate delay (8-12 weeks) may serve as a "biological selection window", allowing for the identification of patients with rapid systemic progression while maximizing local tumor regression, whereas an excessive delay might provide an opportunity for distant dissemination or progression.

Our findings align with the Lyon R90-01 trial [9], which first demonstrated that a 6-8 week interval improves tumor downstaging, and extend this by suggesting that extending the interval to 8-12 weeks may further enhance pCR and DFS. However, the GRECCAR-6 trial [11] did not observe a significant improvement in pCR with an 11-week interval and reported increased surgical complexity. This discrepancy may be explained by differences in patient selection, neoadjuvant regimens, or definitions of pCR across studies. Our continuous dose-response analysis further substantiates the existence of a biologically optimal window, revealing a mathematical peak in pCR at approximately 12.7 weeks. This nonlinear inverted U-shaped relationship indicates that extending the interval initially facilitates radiation-induced tumor apoptosis; however, excessively prolonged intervals (beyond 13 weeks) may allow repopulation of resistant tumor clones or severe fibrosis, thereby diminishing the likelihood of achieving pCR. Regarding DFS, a discrepancy was observed between the SUCRA ranking (favoring 8-12 weeks) and the dose-response peak (5.9 weeks). This divergence is likely attributable to differences in analytical approaches. The categorical NMA is primarily driven by the relatively large number of studies within the 8-12 week interval, resulting in more robust pooled estimates. In contrast, the quadratic regression model is more sensitive to small-sample variability in the early intervals, which can shift the estimated inflection point. Therefore, while the mathematical model suggests a potential earlier peak, the 8-12 week interval remains the most robust and evidence-supported category.

Rather than recommending a single "optimal" interval, our findings support an individualized, risk-adapted approach to surgical timing. For patients who prioritize oncologic cure (e.g., young patients aiming to achieve pCR and potential long-term survival benefit), an interval of 8-12 weeks may be preferable. Conversely,

in patients with low-lying tumors, where sphincter preservation is a major concern, or in those at higher risk of surgical complications, an interval of 6-8 weeks may represent a more pragmatic option. In this context, shared decision-making between clinicians and patients is essential to balance trade-offs between oncologic efficacy and functional outcomes.

It is worth noting that optimizing oncologic outcomes may come at the expense of functional preservation [29]. Although our analysis did not demonstrate statistical difference in SPR between the 6-8 week and 8-12 week intervals, SUCRA rankings highlighted that the 6-8 week interval achieved the highest probability of maximizing sphincter saving [30]. From a surgical perspective, this finding is highly plausible. Performing surgery at 6-8 weeks, prior to the onset of dense radiation-induced fibrosis, may facilitate clearer anatomic plane dissection, thereby reducing surgical complexity [28].

Several limitations should be considered when interpreting our findings. First, substantial clinical heterogeneity existed across the included studies, particularly in neoadjuvant regimens, surgical quality, and outcome definitions. Despite the use of rigorous statistical adjustments, the nature of this analysis remains inherently observational, and residual confounding cannot be entirely excluded.

Second, a significant imbalance in data distribution across surgical interval groups may have influenced the stability of the results. While the 8-12 week interval was supported by 11 studies, extreme intervals were characterized by pronounced data sparsity. For instance, the 4-6 week interval included only two studies, and the 24-28 week interval was derived from a single cohort of 161 patients. Although this prolonged interval was intentionally included to capture a comprehensive clinical landscape, the limited small sample size substantially reduces the reliability of these estimates. This imbalance is reflected in the wide 95% credible intervals seen in the network estimates (e.g., OS for 24-28 week interval) and may have affected the stability of its SUCRA rankings, including the 46.3% probability for recurrence. Therefore, results pertaining to these extreme intervals must be interpreted with great caution. Third, follow-up durations were not uniformly reported across all included studies, which represents an additional source of uncertainty. While these studies were included to maximize the available data for survival analyses, variability or absence of follow-up data may have introduced bias into the estimation of long-term outcomes such as OS and DFS. Fourth, our dose-response meta-analysis was constrained by the use of interval midpoints to approximate continuous exposure, as most original studies only provided categorical interval data (e.g., 6-8 vs. 8-12 weeks). As a result, non-linear curves for sparsely populated intervals may have been underpowered, and the estimated inflection points, like the 12.7-week peak for pCR, should be viewed as robust estimates rather than rigid clinical cutoffs. Finally, the proportion of RCTs was limited, with the majority of included studies being observational in design, which may further affect the strength of causal inference.

Conclusion

Determining the optimal surgical timing after neoadjuvant treatment requires a careful balance between oncologic efficacy and functional preservation. Based on the current synthesis of evidence, an interval of 8-12 weeks is most robustly supported for achieving deeper tumor response, prolonging DFS, and lowering recurrence rates. In contrast, an interval of 6-8 weeks demonstrates the highest probability of improving overall survival and sphincter preservation, although without consistent statistical superiority over the 8-12 week interval in all functional metrics. These findings support an individualized approach to surgical timing, incorporating tumor characteristics, patient comorbidities, and treatment preferences within a shared decision-making framework. Future prospective studies integrating biomarker-driven stratification are warranted to further refine precision-based surgical timing strategies in locally advanced rectal cancer.

Disclosure of conflict of interest

None.

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Table S1. Search strategy

Search number	Query	Search Details	Results
8	(((“Carcinoembryonic Antigen”[Mesh]) OR ((((((((((Carcinoembryonic Antigen[Title/Abstract]) OR (Antigen, Carcinoembryonic[Title/Abstract])) OR (CD66e Antigen[Title/Abstract])) OR (Antigens, CD66e[Title/Abstract])) OR (CD66e Antigens[Title/Abstract])) OR (Antigen, CD66e[Title/Abstract])) OR (carcinoembryonic protein[Title/Abstract])) OR (ce antigen[Title/Abstract])) OR (CEA[Title/Abstract])) OR (protein, carcinoembryonic[Title/Abstract])))) AND ((“Colorectal Neoplasms”[Mesh]) OR ((((((((((((((((((Colorectal Neoplasms[Title/Abstract]) OR (Colorectal Neoplasm[Title/Abstract])) OR (Neoplasm, Colorectal[Title/Abstract])) OR (Neoplasms, Colorectal[Title/Abstract])) OR (Colorectal Tumors[Title/Abstract])) OR (Colorectal Tumor[Title/Abstract])) OR (Tumor, Colorectal[Title/Abstract])) OR (Tumors, Colorectal[Title/Abstract])) OR (Colorectal Cancer[Title/Abstract])) OR (Cancer, Colorectal[Title/Abstract])) OR (Cancers, Colorectal[Title/Abstract])) OR (Colorectal Cancers[Title/Abstract])) OR (Colorectal Carcinoma[Title/Abstract])) OR (Carcinoma, Colorectal[Title/Abstract])) OR (Carcinomas, Colorectal[Title/Abstract])) OR (Colorectal Carcinomas[Title/Abstract])) OR (colorectal tumorigenesis[Title/Abstract])) OR (colorectal tumour[Title/Abstract])) OR (tumour, colorectal[Title/Abstract]))))) AND ((((((((((((((liver metastasis[Title/Abstract]) OR (hepatic metastases[Title/Abstract])) OR (hepatic metastasis[Title/Abstract])) OR (hepatocellular metastasis[Title/Abstract])) OR (liver metastases[Title/Abstract])) OR (liver tumor metastases[Title/Abstract])) OR (liver tumor metastasis[Title/Abstract])) OR (liver tumour metastasis[Title/Abstract])) OR (metastases of the liver[Title/Abstract])) OR (metastasis in liver[Title/Abstract])) OR (metastasis, liver[Title/Abstract])) OR (metastatic hepatocellular[Title/Abstract])) OR (metastatic liver[Title/Abstract])) OR (metastatic liver cell[Title/Abstract]))	(“Carcinoembryonic Antigen”[MeSH Terms] OR (“Carcinoembryonic Antigen”[Title/Abstract] OR “antigen carcinoembryonic”[Title/Abstract] OR ((“Carcinoembryonic Antigen”[MeSH Terms] OR (“Carcinoembryonic”[All Fields] AND “Antigen”[All Fields]) OR “Carcinoembryonic Antigen”[All Fields] OR “CD66e”[All Fields]) AND “Antigen”[Title/Abstract]) OR ((“antigen s”[All Fields] OR “antigene”[All Fields] OR “antigenes”[All Fields] OR “antigenic”[All Fields] OR “antigenically”[All Fields] OR “antigenicities”[All Fields] OR “antigenicity”[All Fields] OR “antigenized”[All Fields] OR “Antigens”[MeSH Terms] OR “Antigens”[All Fields] OR “Antigen”[All Fields]) AND “CD66e”[Title/Abstract]) OR ((“Carcinoembryonic Antigen”[MeSH Terms] OR (“Carcinoembryonic”[All Fields] AND “Antigen”[All Fields]) OR “Carcinoembryonic Antigen”[All Fields] OR “CD66e”[All Fields]) AND “Antigens”[Title/Abstract]) OR “antigen cd66e”[Title/Abstract] OR “carcinoembryonic protein”[Title/Abstract] OR “ce antigen”[Title/Abstract] OR “CEA”[Title/Abstract] OR “protein carcinoembryonic”[Title/Abstract])) AND (“Colorectal Neoplasms”[MeSH Terms] OR (“Colorectal Neoplasms”[Title/Abstract] OR “colorectal neoplasm”[Title/Abstract] OR “neoplasm colorectal”[Title/Abstract] OR “neoplasms colorectal”[Title/Abstract] OR “colorectal tumors”[Title/Abstract] OR “colorectal tumor”[Title/Abstract] OR “tumor colorectal”[Title/Abstract] OR “tumors colorectal”[Title/Abstract] OR “colorectal cancer”[Title/Abstract] OR “cancer colorectal”[Title/Abstract] OR “cancers colorectal”[Title/Abstract] OR “colorectal cancers”[Title/Abstract] OR “colorectal carcinoma”[Title/Abstract] OR “carcinoma colorectal”[Title/Abstract] OR “carcinomas colorectal”[Title/Abstract] OR “colorectal carcinomas”[Title/Abstract] OR “colorectal tumorigenesis”[Title/Abstract] OR “colorectal tumour”[Title/Abstract] OR ((“cysts”[MeSH Terms] OR “cysts”[All Fields] OR “cyst”[All Fields] OR “neurofibroma”[MeSH Terms] OR “neurofibroma”[All Fields] OR “neurofibromas”[All Fields] OR “tumor s”[All Fields] OR “tumoral”[All Fields] OR “tumorous”[All Fields] OR “tumour”[All Fields] OR “Neoplasms”[MeSH Terms] OR “Neoplasms”[All Fields] OR “Tumor”[All Fields] OR “tumour s”[All Fields] OR “tumoural”[All Fields] OR “tumourous”[All Fields] OR “tumours”[All Fields] OR “Tumors”[All Fields]) AND “Colorectal”[Title/Abstract]))) AND (“liver metastasis”[Title/Abstract] OR “hepatic metastases”[Title/Abstract] OR “hepatic metastasis”[Title/Abstract] OR (“hepatocellular”[All Fields] AND “metastasis”[Title/Abstract]) OR “liver metastases”[Title/Abstract] OR “liver tumor metastases”[Title/Abstract] OR “liver tumor metastasis”[Title/Abstract] OR ((“liver”[MeSH Terms] OR “liver”[All Fields] OR “livers”[All Fields] OR “liver s”[All Fields]) AND “tumour metastasis”[Title/Abstract]) OR ((“metastasation”[All Fields] OR “metastasic”[All Fields] OR “metastasing”[All Fields] OR “metastasise”[All Fields] OR “metastasised”[All Fields] OR “metastasises”[All Fields] OR “metastasising”[All Fields] OR “metastasization”[All Fields] OR “metastasizes”[All Fields] OR “metastasizing”[All Fields] OR “neoplasm metastasis”[MeSH Terms] OR (“Neoplasm”[All Fields] AND “metastasis”[All Fields]) OR “neoplasm metastasis”[All Fields] OR “metastase”[All Fields] OR “metastases”[All Fields] OR “metastasize”[All Fields] OR “metastasized”[All Fields]) AND “of the liver”[Title/Abstract]) OR ((“metastasi”[All Fields] OR “neoplasm metastasis”[MeSH Terms] OR (“Neoplasm”[All Fields] AND “metastasis”[All Fields]) OR “neoplasm metastasis”[All Fields] OR “metastasis”[All Fields]) AND “in liver”[Title/Abstract]) OR “metastasis liver”[Title/Abstract] OR “metastatic hepatocellular”[Title/Abstract] OR “metastatic liver”[Title/Abstract] OR “metastatic liver cell”[Title/Abstract])	1,504

7	((((((((((((liver metastasis[Title/Abstract]) OR (hepatic metastases[Title/Abstract])) OR (hepatic metastasis[Title/Abstract])) OR (hepatocellular metastasis[Title/Abstract])) OR (liver metastases[Title/Abstract])) OR (liver tumor metastases[Title/Abstract])) OR (liver tumor metastasis[Title/Abstract])) OR (liver tumour metastasis[Title/Abstract])) OR (metastases of the liver[Title/Abstract])) OR (metastasis in liver[Title/Abstract])) OR (metastasis, liver[Title/Abstract])) OR (metastatic hepatocellular[Title/Abstract])) OR (metastatic liver[Title/Abstract])) OR (metastatic liver cell[Title/Abstract])	"liver metastasis"[Title/Abstract] OR "hepatic metastases"[Title/Abstract] OR "hepatic metastasis"[Title/Abstract] OR ("hepatocellular"[All Fields] AND "metastasis"[Title/Abstract]) OR "liver metastases"[Title/Abstract] OR "liver tumor metastases"[Title/Abstract] OR "liver tumor metastasis"[Title/Abstract] OR (("liver"[MeSH Terms] OR "liver"[All Fields] OR "livers"[All Fields] OR "liver s"[All Fields]) AND "tumour metastasis"[Title/Abstract]) OR (("metastasation"[All Fields] OR "metastasic"[All Fields] OR "metastasing"[All Fields] OR "metastasise"[All Fields] OR "metastasised"[All Fields] OR "metastasises"[All Fields] OR "metastasising"[All Fields] OR "metastasization"[All Fields] OR "metastasizes"[All Fields] OR "metastasizing"[All Fields] OR "neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastase"[All Fields] OR "metastases"[All Fields] OR "metastasize"[All Fields] OR "metastasized"[All Fields]) AND "of the liver"[Title/Abstract]) OR (("metastasi"[All Fields] OR "neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastasis"[All Fields]) AND "in liver"[Title/Abstract]) OR "metastasis liver"[Title/Abstract] OR "metastatic hepatocellular"[Title/Abstract] OR "metastatic liver"[Title/Abstract] OR "metastatic liver cell"[Title/Abstract]	51,546
6	("Colorectal Neoplasms"[Mesh]) OR ((((((((((((((((((Colorectal Neoplasms[Title/Abstract]) OR (Colorectal Neoplasm[Title/Abstract])) OR (Neoplasm, Colorectal[Title/Abstract])) OR (Neoplasms, Colorectal[Title/Abstract])) OR (Colorectal Tumors[Title/Abstract])) OR (Colorectal Tumor[Title/Abstract])) OR (Tumor, Colorectal[Title/Abstract])) OR (Tumors, Colorectal[Title/Abstract])) OR (Colorectal Cancer[Title/Abstract])) OR (Cancer, Colorectal[Title/Abstract])) OR (Cancers, Colorectal[Title/Abstract])) OR (Colorectal Cancers[Title/Abstract])) OR (Colorectal Carcinoma[Title/Abstract])) OR (Carcinoma, Colorectal[Title/Abstract])) OR (Carcinomas, Colorectal[Title/Abstract])) OR (Colorectal Carcinomas[Title/Abstract])) OR (colorectal tumorigenesis[Title/Abstract])) OR (colorectal tumour[Title/Abstract])) OR (tumour, colorectal[Title/Abstract]))	"Colorectal Neoplasms"[MeSH Terms] OR ("Colorectal Neoplasms"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "neoplasm colorectal"[Title/Abstract] OR "neoplasms colorectal"[Title/Abstract] OR "colorectal tumors"[Title/Abstract] OR "colorectal tumor"[Title/Abstract] OR "tumor colorectal"[Title/Abstract] OR "tumors colorectal"[Title/Abstract] OR "colorectal cancer"[Title/Abstract] OR "cancer colorectal"[Title/Abstract] OR "cancers colorectal"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "carcinoma colorectal"[Title/Abstract] OR "carcinomas colorectal"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract] OR "colorectal tumorigenesis"[Title/Abstract] OR "colorectal tumour"[Title/Abstract] OR (("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "Neoplasms"[MeSH Terms] OR "Neoplasms"[All Fields] OR "Tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "Tumors"[All Fields]) AND "Colorectal"[Title/Abstract]))	284,239
5	((((((((((((((((((Colorectal Neoplasms[Title/Abstract]) OR (Colorectal Neoplasm[Title/Abstract])) OR (Neoplasm, Colorectal[Title/Abstract])) OR (Neoplasms, Colorectal[Title/Abstract])) OR (Colorectal Tumors[Title/Abstract])) OR (Colorectal Tumor[Title/Abstract])) OR (Tumor, Colorectal[Title/Abstract])) OR (Tumors, Colorectal[Title/Abstract])) OR (Colorectal Cancer[Title/Abstract])) OR (Cancer, Colorectal[Title/Abstract])) OR (Cancers, Colorectal[Title/Abstract])) OR (Colorectal Cancers[Title/Abstract])) OR (Colorectal Carcinoma[Title/Abstract])) OR (Carcinoma, Colorectal[Title/Abstract])) OR (Carcinomas, Colorectal[Title/Abstract])) OR (Colorectal Carcinomas[Title/Abstract])) OR (colorectal tumorigenesis[Title/Abstract])) OR (colorectal tumour[Title/Abstract])) OR (tumour, colorectal[Title/Abstract])	"colorectal neoplasms"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "neoplasm colorectal"[Title/Abstract] OR "neoplasms colorectal"[Title/Abstract] OR "colorectal tumors"[Title/Abstract] OR "colorectal tumor"[Title/Abstract] OR "tumor colorectal"[Title/Abstract] OR "tumors colorectal"[Title/Abstract] OR "colorectal cancer"[Title/Abstract] OR "cancer colorectal"[Title/Abstract] OR "cancers colorectal"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "carcinoma colorectal"[Title/Abstract] OR "carcinomas colorectal"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract] OR "colorectal tumorigenesis"[Title/Abstract] OR "colorectal tumour"[Title/Abstract] OR (("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "Neoplasms"[MeSH Terms] OR "Neoplasms"[All Fields] OR "Tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "Tumors"[All Fields]) AND "Colorectal"[Title/Abstract])	170,765

4	"Colorectal Neoplasms"[Mesh]	"Colorectal Neoplasms"[MeSH Terms]	233,289
3	("Carcinoembryonic Antigen"[Mesh]) OR ((((((((((Carcinoembryonic Antigen[Title/Abstract]) OR (Antigen, Carcinoembryonic[Title/Abstract])) OR (CD66e Antigen[Title/Abstract])) OR (Antigens, CD66e[Title/Abstract])) OR (CD66e Antigens[Title/Abstract])) OR (Antigen, CD66e[Title/Abstract])) OR (carcinoembryonic protein[Title/Abstract])) OR (ce antigen[Title/Abstract])) OR (CEA[Title/Abstract])) OR (protein, carcinoembryonic[Title/Abstract]))	"Carcinoembryonic Antigen"[MeSH Terms] OR ("Carcinoembryonic Antigen"[Title/Abstract] OR "antigen carcinoembryonic"[Title/Abstract] OR ((("Carcinoembryonic Antigen"[MeSH Terms] OR ("Carcinoembryonic"[All Fields] AND "Antigen"[All Fields]) OR "Carcinoembryonic Antigen"[All Fields] OR "CD66e"[All Fields]) AND "Antigen"[Title/Abstract]) OR (("antigen s"[All Fields] OR "antigene"[All Fields] OR "antigenes"[All Fields] OR "antigenic"[All Fields] OR "antigenically"[All Fields] OR "antigenicities"[All Fields] OR "antigenicity"[All Fields] OR "antigenized"[All Fields] OR "Antigens"[MeSH Terms] OR "Antigens"[All Fields] OR "Antigen"[All Fields]) AND "CD66e"[Title/Abstract]) OR (("Carcinoembryonic Antigen"[MeSH Terms] OR ("Carcinoembryonic"[All Fields] AND "Antigen"[All Fields]) OR "Carcinoembryonic Antigen"[All Fields] OR "CD66e"[All Fields]) AND "Antigens"[Title/Abstract]) OR "antigen cd66e"[Title/Abstract] OR "carcinoembryonic protein"[Title/Abstract] OR "ce antigen"[Title/Abstract] OR "CEA"[Title/Abstract] OR "protein carcinoembryonic"[Title/Abstract])	36,588
2	((((((((((Carcinoembryonic Antigen[Title/Abstract]) OR (Antigen, Carcinoembryonic[Title/Abstract])) OR (CD66e Antigen[Title/Abstract])) OR (Antigens, CD66e[Title/Abstract])) OR (CD66e Antigens[Title/Abstract])) OR (Antigen, CD66e[Title/Abstract])) OR (carcinoembryonic protein[Title/Abstract])) OR (ce antigen[Title/Abstract])) OR (CEA[Title/Abstract])) OR (protein, carcinoembryonic[Title/Abstract])	"carcinoembryonic antigen"[Title/Abstract] OR "antigen carcinoembryonic"[Title/Abstract] OR ((("carcinoembryonic antigen"[MeSH Terms] OR ("Carcinoembryonic"[All Fields] AND "Antigen"[All Fields]) OR "carcinoembryonic antigen"[All Fields] OR "CD66e"[All Fields]) AND "Antigen"[Title/Abstract]) OR (("antigen s"[All Fields] OR "antigene"[All Fields] OR "antigenes"[All Fields] OR "antigenic"[All Fields] OR "antigenically"[All Fields] OR "antigenicities"[All Fields] OR "antigenicity"[All Fields] OR "antigenized"[All Fields] OR "Antigens"[MeSH Terms] OR "Antigens"[All Fields] OR "Antigen"[All Fields]) AND "CD66e"[Title/Abstract]) OR (("carcinoembryonic antigen"[MeSH Terms] OR ("Carcinoembryonic"[All Fields] AND "Antigen"[All Fields]) OR "carcinoembryonic antigen"[All Fields] OR "CD66e"[All Fields]) AND "Antigens"[Title/Abstract]) OR "antigen cd66e"[Title/Abstract] OR "carcinoembryonic protein"[Title/Abstract] OR "ce antigen"[Title/Abstract] OR "CEA"[Title/Abstract] OR "protein carcinoembryonic"[Title/Abstract]	33,900
1	"Carcinoembryonic Antigen"[Mesh]	"Carcinoembryonic Antigen"[MeSH Terms]	16,436

Table S2. The NOS quality score of the included cohort studies

cohort study	Selection of research population				Comparability between groups	Result measurement			score
	Exposure group Representativeness	Non exposure group representativeness	Determination of exposure factors	The endpoint did not occur at the starting point of the study		Ending evaluation	Follow up time	Complete follow-up	
Kammar 2020	1	1	1	1	2	1	1	0	8
Mihmanlı 2016	1	1	1	1	2	1	1	1	9
Jeong 2013	1	1	1	1	2	1	1	0	8
Sirohi 2014	1	1	1	1	2	1	0	0	7
Rombouts 2016	1	1	1	1	2	1	1	0	8
Piva 2022	1	1	1	1	2	1	0	0	7
Amin 2024	1	1	1	1	2	1	1	0	8
Garrer 2016	0	1	1	1	1	1	0	0	5
Roxburgh 2019	1	1	1	1	2	1	0	0	7