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Total neoadjuvant therapy for locally advanced rectal cancer (Protocol)

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Total neoadjuvant therapy for locally advanced rectal cancer (Protocol).
Cochrane Database of Systematic Reviews 2025, Issue 5. Art. No.: CD015590.
DOI: 10.1002/14651858.CD015590.

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[Intervention Protocol]

Total neoadjuvant therapy for locally advanced rectal cancer

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Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 5, 2025.

Citation: Mueller S, Kao Y-S, Kastner C, Chen P-H, Hendricks A, Lee GY, Koehler F, Jhou H-J, Germer C-T, Kang E-NY, Janka H, Ho C-L, Lee C-H, Wiegering A. Total neoadjuvant therapy for locally advanced rectal cancer (Protocol). *Cochrane Database of Systematic Reviews* 2025, Issue 5. Art. No.: CD015590. DOI: 10.1002/14651858.CD015590.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness and safety of total neoadjuvant therapy versus standard therapy in individuals with locally advanced rectal cancer.

BACKGROUND

Description of the condition

Colorectal cancer is the third most common cancer and the third most frequent cancer-related cause of death worldwide (Siegel 2022). Adenocarcinoma localized within 16 cm of the anal verge is defined as rectal cancer; this applies to roughly 40% of all colorectal cancers (Nielsen 2014). Due to its anatomic localization, tumors within the upper third of the rectum are treated using colon carcinoma protocols (Benson 2024; DKG 2019). Tumors in the lower two-thirds of the rectum are treated within a multimodal concept that includes chemotherapy, radiotherapy, and surgery in different sequences and of different intensities (Benson 2024; Nielsen 2014).

Clinical stage and surgical resectability determine the treatment algorithm for rectal cancer. For the determination of the clinical stage, a combination of magnetic resonance imaging (MRI) and rectal endosonography is considered to be the gold standard and provides the most accurate results (Bates 2022; Fernandes 2022; Horvat 2019). For early-stage rectal cancer (clinical stage T1 and T2 without lymph node involvement), curative surgery remains the standard of care (Benson 2024). Locally advanced rectal cancer is described as T3 and T4 tumors or tumors with lymph node metastases (Valentini 2009).

The treatment regimen for locally advanced rectal cancer has evolved since the early 2000s (Weinberg 2024; Wiegering 2014). At present, the recommended therapy for locally advanced rectal cancer consists of preoperative radio-(chemo) therapy, surgery, and postoperative adjuvant chemotherapy (Benson 2024). This treatment leads to pathological downstaging and reduced local recurrence rates, but has no proven positive effect on disease-free and overall survival (Sauer 2004; Sauer 2012; Sebag-Montefiore 2009).

Total neoadjuvant therapy is defined as the completion of chemotherapy with or without radiotherapy, before surgery. After total neoadjuvant therapy, an oncological resection with a total mesorectal excision should be performed, in which all of the mesorectal fat - including all the lymph nodes - should be meticulously excised (Glynne-Jones 2017). If the sphincter muscle is infiltrated by the tumor, it should be removed completely (rectal extirpation) and a permanent stoma inserted (Glynne-Jones 2017).

Description of the intervention

Guidelines recommend a total of six months of systemic chemotherapy in combination with local radiotherapy for locally advanced rectal cancer. This is mostly done as two months of neoadjuvant - that is preoperative - chemotherapy in combination with local radiotherapy, and four months of adjuvant - that is postoperative - chemotherapy (Fokas 2019; Nielsen 2014). Currently, two kinds of preoperative radiotherapy regimens have been proven to be effective. One is short-course radiotherapy, which is composed of a radiation dose of 5 Gray (Gy) daily for five days followed by immediate surgery or systemic chemotherapy (Liao 2022). The other is long-course radio-chemotherapy, which uses daily radiation of 1.8 to 2.0 Gy for up to five to six weeks (average cumulative radiation dose between 45 and 50.4 Gy), combined with 5-fluorouracil-based (5-FU) chemotherapy (Benson 2024; Rodel 2015). These preoperative treatments are intended to reduce the overall tumor size, reduce local recurrence, and, in selected cases, to enable sphincter-preserving surgery.

Adjuvant, postoperative chemotherapy is recommended to complete treatment after surgical resection (Sun 2017). Overall, there are several agents and regimens for perioperative chemotherapy that are proven to reduce the local recurrence rate and cancer-related mortality (Benson 2024; Nielsen 2014; Rodel 2015).

Due to postoperative complications and poor compliance with therapy, less than 50% of eligible patients currently receive the adjuvant chemotherapy that is planned initially and, therefore, do not receive the entire six months of systemic therapy that they should (Glynne-Jones 2014; Khrizman 2013; Petersen 2012; Rodel 2012).

The concept of total neoadjuvant therapy is to complete full-dose systemic chemotherapy, with or without radiotherapy, prior to surgery. Systemic chemotherapy can be given either prior to (induction) or following (consolidation) radiation therapy (Fokas 2019; Johnson 2023). Since the entire therapy takes place before the surgery, there may be an increase in complications during and after the operation. In some cases, people may no longer be eligible for surgery because they tolerated the total neoadjuvant therapy poorly. Additionally, the prolonged preoperative therapy may lead to local tumor growth or development of distant metastases (Ng 2024).

The latest evidence shows that total neoadjuvant therapy in people with locally advanced rectal cancer is expected to deliver a reduction in distant metastasis, a more complete tumor response, and improved disease-free and overall survival (Bahadoer 2021; Cisel 2019; Conroy 2021; Fokas 2022). Furthermore, total neoadjuvant therapy may improve colostomy-free survival by reducing the need for surgery (Cercek 2018; Garcia-Aguilar 2015; Garcia-Aguilar 2022; Verheij 2023).

For the purposes of this review, we will use only studies that have planned at least five cycles of folinic acid, fluorouracil and oxaliplatin (FOLFOX)-based or at least four cycles of oxaliplatin and capecitabine (CAPOX)-based chemotherapy for total neoadjuvant therapy.

How the intervention might work

A strategy of using total neoadjuvant therapy has several theoretical advantages, which include early treatment of micrometastasis and increasing the ratio of people who complete the entire chemotherapy course as planned, both of which lead to a better overall survival rate (Conroy 2024; Weiser 2022). Furthermore, total neoadjuvant therapy can increase response rates and pathological complete response rates due to a prolonged therapy interval, especially for induction radiotherapy and de-escalation of therapies based on response (Zwart 2024).

Why it is important to do this review

Total neoadjuvant therapy has gained extensive popularity in the past few years and numerous observational studies and randomized controlled trials (RCT) have been published (Bahadoer 2021; Conroy 2021; Conroy 2024; Fernandez-Martos 2015; Fokas 2022; Garcia-Aguilar 2015). The American NCCN (National Comprehensive Cancer Network) guidelines (Benson

2024), as well as the German cancer guideline (DKG 2019), have incorporated total neoadjuvant treatment into their standard treatment recommendations for locally advanced rectal cancer due to the evidence that has emerged in recent years (Benson 2024). This Cochrane review will assess the effect of total neoadjuvant therapy and inform the wider clinical community about the efficacy and safety of total neoadjuvant therapy. Furthermore, this study will highlight the areas that require further evidence.

In the context of this review, we will analyze only classical chemotherapy. Studies on this have been published repeatedly for several years; however, a systematic analysis in a Cochrane review has not yet been carried out. New therapeutic approaches in immunotherapy that depend on microsatellite status are also a very interesting field, but, as there is currently limited data for this treatment modality and, as mixing the two therapeutic approaches does not seem sensible to us, we deliberately excluded these from this review.

OBJECTIVES

To assess the effectiveness and safety of total neoadjuvant therapy versus standard therapy in individuals with locally advanced rectal cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include phase II or III RCTs and cluster-RCTs that identify participants prospectively. We will include studies published in any language. We will consider studies regardless of their publication status, if they provide sufficient information. We will exclude non-randomized trials, retrospective studies, case reports, and review articles. We will also exclude cross-over trials because applying two treatment procedures sequentially lacks medical significance for this cancer.

Types of participants

Even though the term "locally advanced rectal cancer" is usually used, a definite international consensus of the condition is lacking. Locally advanced rectal cancer is mainly defined as: primary tumor growth into the mesorectal fat tissue (clinical T3 stage); tumor existence equal to or less than 1 mm of the mesorectal fascia; invasion of contiguous structures (clinical T4 stage); with or without metastasis to regional lymph node (clinical N1/2 stage) (Benson 2024; Horvat 2019). We will include participants who meet any of the above criteria. We will not apply restrictions regarding the setting in which studies take place, which means that we can include studies from all countries and from all levels of care with full demographic diversity.

Inclusion criteria

- Age minimum 18 years
- People with a confirmed diagnosis of locally advanced rectal cancer

Exclusion criteria

- Previous radiation of the pelvis, as this prevents the planned dose of radiotherapy from being delivered
- Pregnancy, as this could lead to deviations in treatment regimens
- Synchronous malignancies, as this could affect survival negatively
- Immune suppression status (human immunodeficiency virus (HIV) infection or administration of immunosuppressant medication), as this could affect survival negatively
- Recurrent rectal cancer, as other treatment options are chosen for this sector of the population
- Stage IV locally advanced rectal cancer, as distant metastases can affect survival negatively

If a study mentions only a subgroup of eligible participants, we will not use the data from this study for the overall analysis, as, even if a large proportion of the participants that the study mentions fulfill the inclusion criteria, this could reduce the applicability of our results.

Types of interventions

Experimental interventions

The core concept of total neoadjuvant therapy is the application of the main portion of systemic chemotherapy prior to planned rectal cancer resection. After surgery, or in the case of clinical complete response, no further therapy is administered. Systemic chemotherapy can be applied alone, or combined with either short-course radiation or long-course radio-chemotherapy. Systemic chemotherapy can be given either prior to (induction) or following (consolidation) radiation therapy. Systemic chemotherapy should be with 5-FU- or oxaliplatin-based regimens.

Control

Neoadjuvant radiotherapy (i.e. long-course or short-course radiation without chemotherapy) or radio-chemotherapy (i.e. radiotherapy with up to two months of chemotherapy, or with less than 50% of total planned chemotherapy dosage), followed by surgical resection including total mesorectal excision plus post-surgical adjuvant systemic chemotherapy (at least 50% of total planned dosage).

Types of outcome measures

We will include all eligible studies that fit our inclusion criteria and conduct quantitative analyses based on our prespecified outcomes, as listed below. If we exclude studies based on outcomes, we will ensure that relevant outcomes are missing due to measurement issues rather than just non-reporting, and establish this through contact with the corresponding author. A current study by the COMET Initiative is currently focusing on the topic of core outcomes in rectal cancer (COMET Initiative 2024). However, this study is not yet available. We selected the following outcomes on the basis of existing research on the topic and the clinical relevance of each outcome.

Primary outcomes

- **Disease-free survival:** defined as the time period after completion of the respective treatment - either total neoadjuvant therapy followed by surgery (experimental arm) or neoadjuvant therapy followed by surgery and adjuvant therapy (control arm) - of locally advanced rectal cancer until recurrence (either local or distant recurrence) or death from any cause. We

will use three-year disease-free survival data first and other time periods as alternatives. We will analyze one-, three- and five-year survival.

Secondary outcomes

- **Overall survival:** the time period between diagnosis and death. We will use the data of the longest median follow-up time. We will analyze one-, three- and five-year survival.
- **Pathological complete response rate:** the percentage of pathological complete response after completion of the respective treatment (i.e. the complete absence of any residual cancer after treatment determined through microscope examination of tissue samples)
- **Clinical complete response rate:** the percentage of clinical complete response after one, three or five years of completion of the respective treatment, defined as participants who, due to complete clinical remission, do not undergo rectal resection but instead undergo a watch-and-wait approach
- **Sphincter-sparing surgery:** the proportion of participants who receive sphincter-sparing surgery
- **Anastomotic leakage rates:** defined as a new defect that occurs in the integrity of the intestinal wall at the colorectal anastomotic site (including suture and staple lines), which leads to communication between the intra- and extraluminal compartments (according to the International Study Group of Rectal Cancer (Rahbari 2010)), within the first 90 days after surgery
- **Overall grade 3 or 4 adverse events:** as defined in the National Institute for Health (NIH) National Cancer Institute's (NCI) 'Common terminology criteria for adverse events' version 5.0, which occur within 90 days after chemotherapy (NIHN 2024)
- **Surgical complications:** classified according to the Clavien Dindo classification (Clavien 2009), which occur within the first 90 days after surgery
- **Quality of life:** assessed using validated quality of life questionnaires at three, six, 12 and 24 months after the end of the cancer treatment

For evaluations in the summary of findings table we will favor the time point after three years for disease-free survival, overall survival, and clinical complete response.

Search methods for identification of studies

The search strategy for identifying suitable studies was developed according to the advice in the *Cochrane Handbook for Systematic Reviews of Interventions* in collaboration with a search specialist (HJ) (Lefebvre 2023).

Electronic searches

We will perform literature searches in the following databases and relevant sources according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2023).

We will search all the following databases from the date of their inception onwards. We will impose no restrictions regarding language of publication or publication status.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library
- MEDLINE Ovid (Ovid MEDLINE(R) ALL 1946 to present)
- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int)

For the search strategy, we will use RCT filters as described in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2023). A recent publication has demonstrated that these filters yield the best search results (Glanville 2020).

For detailed search strategies, see Appendix 1.

Searching other resources

We will identify potentially eligible records and ancillary publications by reviewing the reference lists of retrieved records, which may include various types of information, such as clinical trials, systematic reviews, meta-analyses and health technology assessment reports. To ensure that no potential records are overlooked, we will contact the authors of the included trials to inquire about any additional studies of which they are aware. We will evaluate both abstracts and full-text publications for information, such as participant characteristics, study design, intervention(s), and outcomes.

- **Manual reference search**
  - We will handsearch the bibliographies of ongoing trials, relevant reviews, and the latest treatment guidelines that we identify through our electronic searching for potentially eligible studies for references to other potentially relevant studies.
  - **Conference proceedings:** we will handsearch the following conference proceedings for abstracts published over the last three years relating to potentially relevant studies:
    - *The American Association for Cancer Research* (AACR)
    - *The American Society of Clinical Oncology* (ASCO)
    - *European Society of Medical Oncology* (ESMO)
    - *The American Society for Radiation Oncology* (ASTRO)
    - *The European Society of Therapeutic Radiation Oncology* (ESTRO)
- **Personal contact:** we will contact the lead investigators of relevant studies when only preliminary or interim reports are available, or if the studies do not provide enough information, for example, about basic characteristics and outcomes of interest.

Data collection and analysis

Selection of studies

We will use Covidence reference management software to identify and exclude duplicate records (Covidence). CHL and SM will screen the titles and abstracts of retrieved records and decide whether to assess the full text independently to determine eligibility. When we disagree, we will obtain the full text for group discussion. We will exclude records that do not meet the inclusion criteria. Two reviewers (CK and YNL) will randomly evaluate 20% of excluded records for any misclassifications. We will obtain full-text copies of the remaining abstracts for further review. CHL and SM will independently study those records and select relevant studies. In the case of disagreement, a third author (AW) will thoroughly review the study and judge the discrepancy.

If multiple reports and publications relate to a single study, we will group them together under a single reference ID.

We will include a PRISMA flow chart in the full review to demonstrate details of the number of records retrieved, included and excluded (Moher 2009). Our reasons for the exclusion of studies that readers might expect to see included in the full review will be presented in a "Characteristics of excluded studies" table (Liberati 2009).

Data extraction and management

KU and GYL will independently extract data from the included studies using a form that has been customized for this work according to the specifications in Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2023). We will pilot the form within the review team to ensure its usability. We will contact the corresponding authors of specific studies for supplementary information if necessary. If AH and GYL are unable to achieve a consensus on the inclusion of data, a third reviewer (AW) will be involved for final judgment. After agreement on the extracted data, SM will transfer the data to RevMan (Review Manager, the Cochrane review-writing software) (RevMan 2025), and the input data will be double-checked by CHL.

We will collect the following categories of information for the included studies.

- **General information:** title, author, source, country, publication date, and language of publication
- **Quality assessment:** randomized sequence generation; allocation concealment; condition of blinding (participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting, and others
- **Methods:** trial design (setting, study aims, and dates); source of participants; inclusion and exclusion criteria; comparability of groups at baseline; statistical methods; subgroup analysis; power calculations; length of follow-up; and compliance with assigned treatment
- **Participant characteristics:** eligibility and recruitment method; baseline characteristics (age; sex; number of participants recruited, allocated, and evaluated; initial clinical cancer stage; localization in the rectum; and participants lost to follow-up)
- **Interventions:** main treatment regimens; drugs and dosages; frequency; route of administration; type of surgery; and radiotherapy regimens.
- **Outcomes:** disease-free survival; pathological complete response; total mesorectal excision quality; overall survival or mortality; sphincter-sparing surgery; postoperative complication rates; anastomotic leakage rates; adverse events (grades 3 to 4) requiring discontinuation of treatment; withdrawal rates, including the number of individuals excluded from outcome assessment after randomization and the reasons for their exclusion
- **Others:** sponsorship or funding of study and conflicts of interest of primary investigators

If possible, we will extract data at the study-arm level, rather than summary effects. We will summarize the characteristics of all included studies and present these in the “Characteristics of included studies” table in the full review.

Assessment of risk of bias in included studies

We will use the Risk of Bias 2.0 (RoB 2) assessment tool to evaluate the risk of bias for the included studies for the following outcomes (Sterne 2019), though only seven of these will feature in our summary of findings table.

- Disease-free-survival
- Overall survival
- Pathological complete response
- Clinical complete response
- Sphincter-sparing surgery
- Anastomotic leakage rates
- Overall grade 3-4 adverse events
- Surgical complications
- Quality of life

We will use the RoB 2 Excel tool to implement RoB 2 and present the results as a supplementary material (available on www.riskofbias.info). We will perform all assessments with RoB 2 on the effect of the assignment to the intervention (the intention-to-treat (ITT) effect). Two reviewers (AH and PHC) will independently assess the overall risk of bias for each outcome of each study based on study level. We will consult a third reviewer (AW) to achieve consensus in case of discrepancies between judgments. We will evaluate the following types of bias as mentioned in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023a).

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We will evaluate these types of bias by using the signaling questions recommended in RoB 2 and judge them using the following response options:

- 'yes'
- 'probably yes'
- 'no'
- 'probably no'
- 'no information'

We will follow the algorithms proposed by RoB 2 to judge the possible risk of bias in each domain as ‘low risk of bias’, ‘some concerns’, or ‘high risk of bias’ (as outlined below). Ultimately, we will rate each prespecified outcome in each study, and will judge outcomes and studies that have at least one domain of bias at high risk to be at a high risk of bias overall.

- 'Low risk of bias': all domains for the outcome are at low risk of bias.
- 'Some concerns': at least one domain for the outcome is judged as having some concerns, but no domain is at high risk of bias.
- 'High risk of bias': at least one domain for the outcome is at high risk of bias, or the trial has some concerns for several domains.

If cluster-randomized studies are included, the risk of bias assessment will be adjusted according to the formalities outlined in

Chapter 23.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*. As a key difference, we will evaluate the identification or recruitment bias and participants will be defined as those in whom investigators seek to measure the outcome of interest (Higgins 2023b).

Measures of treatment effect

We will use the results from intention-to-treat designs to calculate risk ratios (RRs) along with their 95% confidence intervals (CIs) for dichotomous outcomes. For time-to-event data analysis, we will employ hazard ratios (HRs) with 95% CIs or standard errors (SEs). In cases of duplicate publications, we will prioritize data with the longest follow-up. For continuous outcomes, we will determine mean differences (MDs) accompanied by 95% CIs. If studies present varying measurement scales for continuous treatment outcomes, we will standardize the results to a uniform scale and estimate standardized mean differences (SMDs) with 95% CIs. We will input data reported on a scale with a consistent direction of treatment effect.

For dichotomous outcomes, our preferred unit of analysis will be the number of participants in each arm. For continuous outcomes, we will assess the means with standard deviations (SDs) and the total number of participants in each arm. If data are available, we will extract and present hazard ratios (HRs) for mortality outcomes. In cases where HRs are not feasible, we will make our best effort to estimate HRs as accurately as possible, utilizing available information and a purpose-built method following the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If our included studies provide HRs, we will utilize HRs rather than RRs or MDs in a meta-analysis.

Unit of analysis issues

The individual participant is the preferred unit of analysis. If RCTs report the outcome at different time points, we will utilize the longest follow-up time point. If there are inconsistencies in time points across studies, we will adopt a clinically essential time point. In multi-arm studies, we will conduct data synthesis by either excluding arms that are not relevant to the prespecified comparison or combining multi-groups that qualify as either the experimental or control intervention to facilitate a single pairwise comparison. If we identify cluster-randomized trials for inclusion, we will perform the analysis at the allocation level. The data will be analyzed as if each cluster were a single individual, using a summary measure from each cluster (Higgins 2023c). We will not include cross-over trials.

Dealing with missing data

We will deal with missing data in accordance with Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023c). We will contact the corresponding authors of the included studies to request any relevant information that is not reported in the publications. If the number of study participants for a given outcome is not addressed, we will use the number of individuals randomized per intervention arm as the denominator.
If percentages only are provided for dichotomous outcomes, we will derive the numbers of participants from these, though discrepancies may arise in the case of rounded percentages.

We will account for missing means and standard deviations (SD) data as advised in Chapter 7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2023), and we will impute these using the method of Furukawa and colleagues (Furukawa 2006). This method uses a regression equation to predict missing SD values based on other available variables. The imputation takes into account the uncertainty in the imputation process; we will perform sensitivity analyses to assess the impact of the imputation on the results. If outcomes are only presented graphically, not numerically, we will gauge the missing data from figures if feasible. For missing data that cannot be found using the aforementioned methods, we will first determine whether the data are 'missing at random' or 'not missing at random'. While 'missing at random' is typically irrelevant for analysis results, not 'missing at random' is relevant, as it means that an analysis based solely on the available data, typically, will be biased. Publication bias and selective reporting bias inherently produce data that are not 'missing at random', and attrition and exclusions of individuals within studies often contribute to this as well (Deeks 2023).

We will explore the potential influence of missing data on the findings of our meta-analysis in the discussion section.

Assessment of heterogeneity

We will assess clinical heterogeneity, methodological diversity, and statistical heterogeneity separately. We will evaluate clinical factors of heterogeneity, including participants' basic demographics and specific interventions, for any significant variations across RCTs.

We will conduct analysis to assess potential divergence among studies due to methodological factors, such as the implementation of blinding and concealment of allocation sequences. Additionally, we will examine variations in the definition and measurement of measurements across studies to determine if they contribute to significant heterogeneity in the observed intervention effects.

If we recognize substantial statistical heterogeneity (I^2 > 50%), we will demonstrate it and probe possible causes through prespecified subgroup analyses (Deeks 2023).

The degree of heterogeneity is defined as listed below:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will assess inter-study variance in a random-effects meta-analysis by calculating the Tau^2 estimate as well. If excessive statistical heterogeneity is not explained by subgroup or sensitivity analysis, we will not pool the outcome results into meta-analyses, but we will provide a narrative description of the study consequences.

Assessment of reporting biases

If we include at least 10 trials, we will demonstrate any reporting biases graphically in funnel plots and apply statistical testing using a linear regression analysis for all outcomes (Boutron 2023). We will compare funnel plots of treatment effect with trial precision to illustrate any visual asymmetry that would indicate the possibility of selection bias (the selective publication of trials with positive findings) or small-study bias (Egger 1997). We will set a P value less than 0.1 as significant for this test (Sterne 2019).

Data synthesis

Meta-analysis of numerical data

We will perform data analysis as described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* if our included studies are clinically and methodologically homogeneous. We will input data into RevMan (RevMan 2025). We will summarize the outcomes by adopting both fixed-effect and random-effects models. We will conduct the random-effects model as a primary analysis and then use the fixed-effect model in sensitivity tests. We will interpret the results of random-effects meta-analyses with due consideration of the thorough distribution of treatment effects. Additionally, we will use statistical analyses in accordance with the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023).

We will analyze binary outcomes using the Mantel–Haenszel statistics method. For measuring continuous data, we will adopt the inverse variance statistic model. We will use the generic inverse variance method for analyzing time-to-event outcomes.

Synthesis using other methods

We will deal with and report outcomes that cannot be pooled into a meta-analysis by following guidance in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* to enable synthesis without meta-analysis (McKenzie 2023). If the outcome data provided do not allow quantitative assessment (e.g. due to a lack of hazard ratios), we will provide a narrative summary of results of each included trial within tables for synthesizing studies without meta-analysis (McKenzie 2023).

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analyses and determine the influence of subgroups on disease-free survival and pathological complete response rate. The following subgroups will be evaluated:

- short-course radiotherapy or long-course radiochemotherapy; and
- systemic chemotherapy with induction or consolidation radiation design.

We assume that such relevant changes in the treatment concept have an influence on patient outcome.

We assume that the following factors have an influence on heterogeneity and can affect the response to therapy. For this reason, the following subgroup analyses will be carried out if meta-analyses show substantial statistical heterogeneity:

- total mesorectal excision versus no total mesorectal excision;
- type of chemotherapy; and
- tumor localization in the rectum: lower versus middle third of the rectum.

Sensitivity analysis

We will test the robustness of our results by using a fixed-effect model for pairwise meta-analysis. We will conduct sensitivity tests to assess the robustness of our analyses.

The primary analysis will encompass all studies, irrespective of their risk of bias. In a subsequent step, we will exclude studies with a high risk of bias and compare the results to those of the primary analysis. This is further explained in Data synthesis.

In the case of missing data obtained by imputation methods, we will perform sensitivity analyses to ensure that the imputed data are robust.

We will use the domains of ROB 2 to assess bias (Deeks 2023; Higgins 2023a).

Summary of findings and assessment of the certainty of the evidence

This study aims to compare total neoadjuvant therapy with conventional neoadjuvant radio-chemotherapy. We will present a summary of findings table that outlines key evidence for the primary results. This table will offer crucial details about the magnitude of the estimated treatment effect in relative terms, the number of individuals and studies addressing each essential outcome, and the overall confidence ranking in effect estimates for each outcome (Guyatt 2011; Schünemann 2023).

We will assess the certainty of the main body of evidence for each outcome. We will utilize the GRADEprofiler Guideline Development Tool software (GRADEpro GDT) to judge the certainty of the evidence based on Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2023). We will consider the following domains:

- risk of bias;
- inconsistency;
- indirectness;
- imprecision; and
- publication bias.

We will follow the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions*, which takes into account fields related to both internal validity and external validity, such as consistent direction of results (Schünemann 2023). Three independent review authors (CHL, SM and CTG) will rank the certainty of each outcome. In case of disagreements, a fourth reviewer (AW) will hold a group discussion to resolve the discrepancy.

We will downgrade the evidence level by one level for serious concerns or by two levels for very serious concerns for each outcome based on the five GRADE domains.

For each scenario, if there is no identified reason for downgrading the certainty of evidence, it will be categorized as 'no limitation' or 'not serious'. We will describe decisions to downgrade the certainty of studies in footnotes in the summary of findings table, and will provide comments to help readers to understand the review better, if necessary.

We will integrate the overall RoB 2 judgment into the GRADE assessment, as the risk of bias plays a crucial role in shaping the quality of evidence in the GRADE evaluation. We will summarize our judgments in the summary of findings tables and present the following outcomes:

- disease-free-survival (three-year survival);

- overall survival (three-year survival);
- pathological complete response (at the time of the primary operation);
- clinical complete response (after three years);
- sphincter-sparing surgery (at the time of the primary operation);
- anastomotic leakage rates (within the first 90 days after surgery); and
- overall grade 3 to 4 adverse events (within the first 90 days after therapy).

ACKNOWLEDGEMENTS

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Jacob Rosenberg, University of Copenhagen, Herlev Hospital, Centre for Perioperative Optimization, Denmark;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sue Marcus, Cochrane Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Addie-Ann Smyth, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Elizabeth Royle, Cochrane Central Production Service.

Peer-reviewers (provided comments and recommended an editorial decision):

- Tarik Sammour, Associate Professor, Royal Adelaide Hospital (clinical/content review);
- J Joshua Smith, MD, PhD, FACS (clinical/content review);
- Dr Denny Mathew John, Assistant Professor Community Medicine, Saveetha Medical College and Hospital, Chennai SIMATS (Saveetha Institute of Medicine and Technical Sciences) (consumer review);
- Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review);
- Jo Platt, Central Editorial Information Specialist (search review).

An additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

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APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library
#1 MeSH descriptor: [Rectal Neoplasms] explode all trees
#2 ((colorectal or colo-rectal or colorectum or colo-rectum or rectal or rectum or anal or anus) NEAR/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)):ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Neoadjuvant Therapy] this term only
#5 MeSH descriptor: [Chemoradiotherapy] this term only
#6 MeSH descriptor: [Radiotherapy] explode all trees
#7 MeSH descriptor: [Combined Modality Therapy] this term only
#8 (total NEXT neoadjuvant NEXT therap*):ti,ab,kw
#9 (TNT):ti,ab,kw

(Continued)

#10 ((neoadjuvant near/3 (chemotherap* or therap* or treatment* or chemoradiation* or chemo-radiation* or chemoradiotherap* or chemo-radiotherap* or radiochemotherap* or radio-chemotherap* or radiotherap* or radio-therap* or radiat* or irradiat*))):ti,ab,kw

#11 (((combined NEXT modality NEXT therap*) or (multimodal NEXT treatment*) or (multi-modal NEXT treatment*) or (multimodal NEXT therap*) or (multi-modal NEXT therap*))):ti,ab,kw

#12 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 #3 and #12

#14 #13 in Trials

MEDLINE (Ovid)

1 exp Rectal Neoplasms/
2 ((colorectal or colo-rectal or colorectum or colo-rectum or rectal or rectum or anal or anus) adj3 (carcinom* or neoplas* or adeno-carcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
3 1 or 2
4 Neoadjuvant Therapy/
5 Chemoradiotherapy/
6 exp Radiotherapy/
7 Combined Modality Therapy/
8 total neoadjuvant therap*.mp.
9 TNT.tw.
10 (neoadjuvant adj3 (chemotherap* or therap* or treatment* or chemoradiation* or chemo-radiation* or chemoradiotherap* or chemo-radiotherap* or radiochemotherap* or radio-chemotherap* or radiotherap* or radio-therap* or radiat* or irradiat*)).mp.
11 (combined modality therap* or multimodal treatment* or multi-modal treatment* or multimodal therap* or multi-modal therap*).mp.
12 or/4-11
13 3 and 12

[Cochrane Handbook RCT filter, sensitivity-maximizing version (Lefebvre 2023)]
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 randomi?ed.ab.
17 placebo.ab.
18 drug therapy.fs.
19 randomly.ab.
20 trial.ab.
21 groups.ab.
22 or/14-21
23 exp animals/ not humans/
24 22 not 23
25 13 and 24

WHO ICTRP Search Portal (Standard search)

((colorectal OR colo-rectal OR colorectum OR colo-rectum OR rectal OR rectum OR anal OR anus) AND (carcinom* OR neoplasm* OR adenocarcinom* OR cancer* OR tumor* OR tumour* OR sarcom*) AND (total neoadjuvant OR TNT OR neoadjuvant) AND (chemotherap* OR therap* OR treatment* OR chemoradiation OR chemo-radiation OR chemoradiotherap* OR chemo-radiotherap* OR radiochemotherap* OR radio-chemotherap* OR radiotherap* OR radio-therap* OR radiat* OR irradiat* OR combined modality therap* OR multimodal treatment* OR multi-modal treatment* OR multimodal therap* OR multi-modal therap*))

ClinicalTrials.gov (Expert search)

((colorectal OR colo-rectal OR colorectum OR colo-rectum OR rectal OR rectum OR anal OR anus) AND (carcinoma OR neoplasms OR adenocarcinoma OR cancer OR tumor OR tumour OR sarcoma)) AND ((total neoadjuvant OR TNT OR neoadjuvant) AND (chemotherapy OR therapy OR treatment OR chemoradiation OR chemo-radiation OR chemoradiotherapy OR chemo-radiotherapy OR radiochemotherapy OR radio-chemotherapy OR radiotherapy OR radio-therapy OR radiation OR irradiation OR combined modality therapy OR multimodal treatment OR multi-modal treatment OR multimodal therapy OR multi-modal therapy))

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DECLARATIONS OF INTEREST

Sophie Mueller: no conflicts of interest

Yung-Shuo Kao: no conflicts of interest

Carolin Kastner: no conflicts of interest

Po-Huang Chen: no conflicts of interest

Anne Hendricks: no conflicts of interest

Gin Yi Lee: no conflicts of interest

Franziska Koehler: no conflicts of interest

Hong-Jie Jhou: no conflicts of interest

Christoph-Thomas Germer: no conflicts of interest;

Yi-No Kang: no conflicts of interest

Heidrun Janka: no conflicts of interest

Ching-Liang Ho: no conflicts of interest

Cho-Hao Lee: no conflicts of interest

Armin Wiegering: no conflicts of interest

SOURCES OF SUPPORT

Internal sources

- None, Other

  No internal sources of support were used

External sources

- None, Other

  No external sources of support were used