

BMJ Open Toxicities and outcomes of neoadjuvant treatment in elderly patients with locally advanced rectal cancer: a scoping review protocol

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ABSTRACT

Introduction Colorectal cancer remains the second leading cause of cancer-related death in 60–79 years old and the third leading cause of death in patients aged 80 and above. Rectal cancer accounts for approximately a third of colorectal cancer diagnoses. The current standard of care for managing locally advanced rectal cancer involves a multimodal combined approach with neoadjuvant treatment, surgery with total mesorectal excision and adjuvant chemotherapy. Neoadjuvant treatment can be in the form of short-course radiotherapy, long-course concurrent radiotherapy with chemotherapy or total neoadjuvant chemotherapy with concurrent chemoradiotherapy followed by chemotherapy. This scoping aims to assess the toxicity and outcome of the different neoadjuvant treatment modalities in elderly patients.

Methods and analysis We will use Arksey and O'Malley's five scoping review methodology framework stages. Searches will be conducted in Ovid Medline, Embase, Cochrane database and CINAHL. In addition, the researcher will hand search for all registered trials, using a combination of terms such as "locally advanced rectal cancer", "neoadjuvant treatment", and "elderly patients." Two independent reviewers will screen titles and abstracts and then full text based on predefined inclusion and exclusion criteria. Publications will be extracted using a customised data extraction tool to include study characteristics, research topics, exposures and outcomes.

Ethics and dissemination Ethics approval is not required as the data will be collected from the existing literature. The findings of this study will help with future clinical research on the topic. We will publish the findings of this review in a peer-reviewed journal and present them at academic conferences targeting geriatric oncology service providers.

INTRODUCTION

Colorectal cancer remains the second leading cause of cancer-related death in 60–79 years old and the third leading cause of death in patients aged 80 and above. Rectal cancer accounts for approximately one-third of colorectal cancer diagnoses.¹ Incidence of rectal cancer is higher in older age with a mean age at the time of diagnosis of 68

Strengths and limitations of this study

- A comprehensive literature search strategy of Cochrane Central Register of Controlled Trials, Embase, CINAHL, Ovid Medline and databases for registered cancer trials will be used to capture all the relevant literature.
- A blind review will be conducted to ensure rigorous and reliable application of the inclusion and exclusion criteria.
- The review will be limited to English rather than non-English articles or translations of non-English articles.
- Our review may not include all relevant articles or studies published and detected by database search, as some may not be accessible.

years for men and 72 years for women.¹ With an increasing life expectancy globally, the number of elderly patients with rectal cancer is likely to increase.²

The theory behind the increasing incidence of colorectal cancer with age is that molecular and pathophysiologic changes occurring throughout life progressively modify the molecular homeostasis of colonic epithelial cells leading to neoplasia.^{3–4} Animal studies have shown that DNA damage increases in older rodents, suggesting frequent stochastic cellular insult.^{5–7} Ageing also increases epithelial proliferation in rodents and humans.^{4,8}

The management of locally advanced rectal cancer involves a multimodal combined approach.⁹

The current standard of care consists of neoadjuvant long-course chemoradiotherapy or short-course hypofractionated radiotherapy followed by surgery (total mesorectal excision) and adjuvant fluorouracil-based chemotherapy.^{9–10}

The neoadjuvant treatment effectively reduces tumour burden before curative

surgery, leading to pathological downstaging, better surgical outcomes and long-term local control.^{11–13}

Neoadjuvant long-course chemoradiation is associated with improved local control and reduced toxicity compared with postoperative chemoradiation.^{13 14} National Comprehensive Cancer Network guidelines recommended preoperative concurrent chemoradiotherapy as a standard of care for stage 2/3 locally advanced rectal cancer.¹⁵ Clinical trials (FFCD 92-03 and EORTC 22921) showed significant improvement in the complete pathological response and local control rate staging with preoperative concurrent chemoradiotherapy compared with preoperative radiotherapy alone.^{11 14 16}

Recently, total neoadjuvant treatment (TNT) has become a new standard of care for high-risk stage 2 and stage 3 rectal cancers and has been adopted by many cancer institutions.^{17 18} This approach involves the addition of induction or consolidation chemotherapy to standard neoadjuvant chemoradiotherapy or radiotherapy. Randomised phase III trials of TNT in locally advanced rectal cancer (RAPIDO and PRODIGE 23) showed better short-term and long-term outcomes with TNT as compared with standard neoadjuvant long-course chemoradiotherapy or short-course radiotherapy.¹⁸

The benefits of neoadjuvant treatment come at the cost of toxicities and reduced quality of life associated with systemic therapy and local pelvic radiotherapy.^{19 20} It is thought these toxicities are often understated due to the short-term outcomes reported in most clinical trials. Elderly patients have historically been disproportionately under-represented in clinical trials that have guided current practice guidelines.^{21 22} Management strategies employed in elderly patients are typically similar to those undertaken in younger patients, without explicit recommendations to guide management approach patients of advanced age with associated frailty.²³

Furthermore, frailty, age-related health problems such as cardiovascular disease, chronic kidney disease, cognitive and functional decline, and polypharmacy may interfere with treatment delivery and affect the outcome of elderly patients with cancer.^{21 22}

The role and tolerability of neoadjuvant chemoradiotherapy or radiotherapy in the elderly are still controversial. Many studies have evaluated neoadjuvant radiotherapy–chemotherapy in elderly patients with rectal cancer, but the results of these studies were discordant.^{24–27} Preoperative short-course radiotherapy (PSCRT) might be associated with a lower rate of toxicities and better quality of life outcomes compared with the standard preoperative long-course chemoradiotherapy (PLCCRT).^{28 29} Ma *et al* suggested that PSCRT is associated with fewer toxicities and could be considered the treatment of choice in the elderly population when the complete response is not the primary aim; PLCCRT is associated with better pathological complete response.^{28 29} After neoadjuvant treatment, elderly and frail patients might have a poor physical condition, and a delay in surgery may enable time for recovery from treatment-related toxicity and improve

their general condition;²⁹ the meta-analysis by Wu *et al* analysed five studies comparing immediate surgery (<4 weeks) and delayed surgery (>4 weeks) after PSCRT. The delayed surgery group had a higher pathological response and fewer postoperative complications; the survival rate, sphincter preservation rate and R0 resection rate were similar between the two groups.³⁰ No previous scoping reviews were conducted on the neoadjuvant treatment only or the TNT in elderly patients.

As the incidence of rectal cancer in the elderly population increases, it is critical to evaluate whether current recommendations on treatment strategies with multimodality for the general population can be employed safely in the older patients, with the same benefits. This scoping review aims to assess the toxicity and the outcome of the currently available modalities of neoadjuvant treatment of rectal cancer in elderly patients, including when treatments are modified or discontinued due to adverse outcomes. The preliminary literature search revealed a lack of consensus in the management of rectal cancer in the elderly. We aim to clarify the literature on outcomes of neoadjuvant treatment to help determine the best management approach in this cohort of the population and identify gaps in the evidence available, including study types. Scoping reviews are considered appropriate if the intent is to scope the literature, explore the research conducted and refine/clarify concepts. The review will encompass studies that may have reported toxicities and adjustments to treatments related to older age, quality of life, or reduced disability or survival.

This review can also provide methodological support to researchers conducting an outcomes analysis to assess neoadjuvant treatment effectiveness and adherence in a real-world context. It can also further our understanding of how neoadjuvant treatments can affect or support older people with locally advanced rectal cancer.

METHODS AND ANALYSIS

We will use a research approach that follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR).^{31 32} This was identified as a suitable research methodology to help understand the literature. We want to go beyond the effectiveness of neoadjuvant treatments, explore regimens to accommodate the heterogeneous elderly population and the nature of neoadjuvant therapy approaches in older rectal cancer patients and patient-related outcomes. Given that this population is not routinely included in randomised controlled trials, we include non-randomised studies.

The scoping review will be guided by the methodological five-step framework developed by Arksey and O'Malley (identification of the research question, identification of relevant studies, selection of studies, extracting and charting the results, collating, summarising and reporting the results, and consultation with stakeholders (optional)) to ensure rigour in our approach.³³

Table 1 Search terms and keyword

Neoadjuvant	Rectal cancer	Cancer	Elderly
“Neoadjuvant Radiotherapy”	Rectum	Tumour,	Old age
“Neoadjuvant Chemoradiotherapy”	Rectal	Tumour	Frail patients
“Total neoadjuvant”	LARC	Neoplasm	Advanced age
Preoperative treatment	“Locally advanced Rectal	Malignancy	Elderly
Concurrent chemoradiotherapy	cancer”		Frailty
			Aged
			Old adult
			Geriatric

Stage 1: identifying the research question

We defined the research questions for the scoping review by conducting a preliminary literature search. We then identified main concepts using the population (or participants)/concept/context approach recommended by Joanna Briggs Institute.³⁴ Population: rectal cancer patients ≥70 years old, concept: treatment and context: high-income countries. The study will synthesise the literature on neoadjuvant treatment in locally advanced rectal cancer in the elderly population above 70 years. The review will cover all types of neoadjuvant, including short-course radiotherapy, concurrent chemoradiotherapy and total neoadjuvant chemotherapy.

This review aims to answer the following research questions:

What are the toxicities associated with different approaches to neoadjuvant treatment?

What is the treatment outcome in terms of complete pathological response and survival?

How has neoadjuvant treatment been integrated with other models of care/treatments in elderly patients with locally advanced rectal cancer?

Stage 2: identify relevant studies

We will retrieve all journal articles published in the English language. We will conduct a systematic search of the following database: Cochrane Central Register of Controlled Trials, Embase, CINAHL, Ovid Medline and

databases for registered cancer trials such as clinicaltrials.gov, WHO trial registry (<https://trialsearch.who.int/>) and Clinicaltrialsregister.eu. We have identified search terms that will include key terms related to “locally advanced rectal cancer”, “neoadjuvant treatment”, “elderly patients” as shown in [table 1](#). These search terms will be updated to include subject heading terms adapted across databases and with the advice of a librarian, [table 2](#).

Stage 3: selection of studies

Selected studies will be imported into Rayyan software, which will be used to identify duplicate papers. Next, screening titles and abstracts will be carried out.³⁵

Initially, two reviewers will screen titles and abstracts independently to assess relevance using the inclusion and exclusion criteria. Reviewers will discuss their results after the screen is completed, disagreements will be attempted first by the two reviewers, and if necessary, a third member of the research team will be consulted to reach an agreement. The second stage will begin by performing a full-text review to determine which articles meet inclusion criteria. The inclusion and exclusion criteria will be refined in an iterative process to find potentially eligible studies for the review. [Table 3](#) provides an overview of the eligibility criteria.

Study inclusion criteria consist of different methodologies (randomised and non-randomised cohort trials, systematic reviews with or without meta-analyses, and

Table 2 Example of search strategy for Ovid Medline database

	Keyword	
1	Neoadjuvant	(“neoadjuvant treatment” or “Neoadjuvant radiotherapy” or “neoadjuvant chemoradiotherapy” or “preoperative treatment” or “total neoadjuvant treatment” or “concomitant treatment”).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2	Rectal cancer	(“Rectal cancer.ti” or “rectal tumour.ti” or “rectal neoplasm.ti” or “locally advanced rectal cancer.ti” or “rectal tumour” or “rectal cancer”).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	Elderly	(elderly or old or elder\$ or aged or geriatric or frail or “elderly patients” OR elderly” or geriatr*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4		1 and 2 and 3

Table 3 Eligibility criteria

Criteria	Inclusion	Exclusion	Justification
Population	Human studies; elderly 70 years and older	Animal studies	Interested in clinical management
Language	English	Non-English studies	Reviewers only speak English
Time	No publication date restriction	NA	When the term #neoadjuvant is used in the literature
Study topic	Focus on the topic on the neoadjuvant treatment of locally advanced rectal cancer in elderly patients (70 years old and older).	Studies on stage 4 rectal cancer are excluded	
Study design	Randomised or non-randomised cohort studies and systematic reviews with or without meta-analysis	Studies on colorectal cancer not including information on rectal cancer separately are not included	

retrospective cohort studies) on the subject of neoadjuvant treatment of locally advanced rectal cancer in the elderly population (≥ 70 years old), published in the English language. We anticipate that the papers identified as relevant will be heterogeneous in terms of patient mix and definitions. Our inclusion criteria are therefore broad. Colon cancer studies and articles that will not meet the quality check will be excluded. The scoping review will also exclude studies with patients younger than 70, case reports, books, letters to the editor and abstracts for conferences.

Quality assessment

The quality of the articles related to randomised control trials will be assessed using the AMSTAR V.2 tool, which evaluates overall quality. A score of 8 or higher is considered high quality, 4 to 7 is moderate quality and 0–3 is low quality.³⁶ For non-randomised cohort studies, we will use the Newcastle-Ottawa Scale.³⁷

Stage 4: charting the data

Two reviewers will independently extract data from included studies using a data extraction form (Excel sheet). Information about study characteristics and findings, including study design, intervention and outcomes,

will be entered in the charting form, [table 4](#). Charting data will be iterative, and the charting sheet will be continually updated.

Stage 5: collecting, synthesising and reporting the results

The extracted results will be synthesised and reported under the key research questions. We will present a narrative summary including the grade of toxicities associated with different neoadjuvant treatment modalities and pathological responses. The findings will be organised methodological design, key findings and gaps in the literature. Data from separate trials may be combined for meta-analysis if interventions, outcome measures and demographics are similar. The reporting will be compliant with the PRISMA-ScR 22-item checklist.³²

ETHICS AND DISSEMINATION

This scoping review aims to map the existing literature that discusses neoadjuvant treatment of rectal cancer in the elderly population. The findings of this review will be used for further studies and systemic reviews that aim to identify specific approaches on how to manage elderly patients with locally advanced rectal cancer (LARC) best

Table 4 Data extraction framework

Bibliometrics	General study details	Other findings, limitations and quality issues
Authors Title Source Year of publication Institution/country of origin	Study design and methodology Population: ▶ Sample size ▶ Median age ▶ Gender ▶ Eastern Cooperative Oncology Group (ECOG) performance status Intervention: ▶ Types of neoadjuvant treatment, doses and duration Outcomes: ▶ Toxicities and grade of toxicities ▶ Pathological response and survivals	Other findings include dose reduction, treatment interruption, or delay in surgical resection due to treatment toxicities. Any reported limitations or quality issues with study methodologies

preoperatively. The review methodology reviews and collects data from publicly available published studies. Therefore, it does not require ethical approval. The findings will be published in peer-reviewed journals and presented at relevant conferences

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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