National Cancer Control Programme

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Neoadjuvant treatment of patients with locally advanced rectal cancer

Draft National Clinical Guideline

XXXXXXX 2024

HSE National Clinical Guideline:
Neoadjuvant treatment of patients with rectal cancer

National Policy ☐ National Procedure ☐ National Protocol ☐ National Guideline ☐
National Clinical Guideline ☒

DOCUMENT GOVERNANCE [1]	
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Lead responsibility for national monitoring and audit:	Hospital/Cancer Centre/Colorectal Tumour Conference
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Additional headings can be inserted as required	

DOCUMENT MANAGEMENT [2]			
Date effective from:			
Date set for next review:			
Your Reference No: *(if applicable)*		Click or tap here to enter text.	
Current version no:	Click or tap here to enter text.	**Archived version no:**	Click or tap here to enter text.
Note: Original document is Version 0. First revision is Version 1. Second revision is Version 2, and so on.			
Note: HSE National 3PGs should be formally reviewed every 3 years, unless new legislative/regulatory or emerging issues/research/technology/audit etc. dictates sooner.			

[1] Records the senior management roles involved in the governance and development of the document.

[2] Records the control information about the document.

VERSION CONTROL UPDATE [3]			
Version No.	**Date reviewed**	**Section numbers changed**	**Approved by**
		(Insert additional lines as required)	
Document management notes:			

PUBLICATION INFORMATION [4]
Title:
Neoadjuvant treatment of patients with rectal cancer
Topic:
Rectal Cancer
National Group:
National Cancer Control Programme
Short summary:
Evidence-based recommendations on the neoadjuvant treatment of patients with locally advanced rectal cancer.
Description:
The purpose of this National Clinical Guideline is to provide evidence based recommendations on the neoadjuvant treatment of patients with rectal cancer through the integration of the best research evidence with clinical expertise, patient values and experiences.

[3] Records details when a document is reviewed, even if no changes are made.

[4] Records the document information required for publication on the HSE National Central Repository.

Disclaimer

This guideline ("the Guideline") was developed by a multidisciplinary Guideline Development Group ("the Group") and is based upon the best clinical evidence available together with the clinical expertise of the Group members. The Guideline supersedes all previous Health Service Executive (HSE), National Cancer Control Programme (NCCP), and National Clinical Effectiveness Committee (NCEC) guidelines for the diagnosis and staging of patients with locally advanced rectal cancer. The NCCP is part of the HSE and any reference in this disclaimer to the NCCP is intended to include the HSE. Please note, the Guideline is for guidance purposes only. The appropriate application and correct use of the Guideline is the responsibility of each health professional. The Group's expectation is that health professionals will use clinical knowledge and judgment in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgment in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary. The NCCP accepts no liability nor shall it be liable, whether arising directly or indirectly, to the user or any other third party for any claims, loss or damage resulting from any use of the Guideline.

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Table of contents

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1 Background

1.1 Purpose

The purpose of this National Clinical Guideline is to provide evidence based recommendations on the neoadjuvant treatment of patients with rectal cancer through the integration of the best research evidence with clinical expertise, patient values and experiences. This guideline aims to address areas of care with new and emerging evidence, reduce variation in practice, and improve patient experience and service delivery.

1.2 Mandate

The National Cancer Strategy 2017-2026 (Department of Health, 2017) states that: "The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards" (recommendation 37).

1.3 Scope

The scope of the guideline is to provide clinical recommendations on the neoadjuvant treatment of patients with locally advanced rectal cancer.

1.4 Target audience

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with rectal cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with rectal cancer and their significant others. An accompanying Plain Language Summary of this guideline is available in Appendix VI: Plain Language Summary.

While the CEO, General Manager and the Clinical Director of the cancer centre/hospital have corporate responsibility for the implementation of the recommendations in this guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

1.5 Target population

Patients that are covered by this guideline are:

- Adults (18 years or older) that have a suspected diagnosis of rectal cancer.
- Adults with newly diagnosed early and locally advanced rectal cancer.

2 National Clinical Guideline

2.1 Clinical question: In patients diagnosed with locally advanced operable rectal cancer, are there subgroups of patients that should be considered for neoadjuvant therapy?

Evidence summary

Ten randomised controlled trials (Schrag et al., 2023 - PROSPECT, Mei et al., 2023 - CONVERT, Garcia-Aguilar et al., 2022 - OPRA, Jin et al., 2022 - STELLAR, Bahadoer et al., 2021 - RAPIDO, Conroy et al., 2021 - PRODIGE, Fokas et al., 2019- CAO/ARO/AIO-12, Kim et al., 2018 - KCSG CO 14-03, Bujko et al., 2004, Fernandez-Martos et al., 2015 - GCR) and seven international guidelines (National Comprehensive Cancer Network, 2024, Goldberg, 2024, Willett, 2024, Hofheinz et al., 2022, You et al., 2020, Gérard et al., 2017, Glynne-Jones et al., 2017) addressed this clinical question.

Treatment for locally advanced rectal cancer may involve neoadjuvant chemoradiotherapy followed by surgery and then adjuvant systemic chemotherapy. National Clinical Guideline No.25 Diagnosis, staging and treatment of patients with rectal cancer (Department of Health, 2020) recommended that patients with stage III rectal cancer should be considered for preoperative short-course radiotherapy or chemoradiotherapy.

The evidence base for this recommendation is evolving, and while preoperative short-course radiotherapy or chemoradiotherapy is still suitable for some patients, recent trials have explored administering systemic chemotherapy, either alone or alongside radiotherapy, prior to surgery. Eight of these trials explored the concept of total neoadjuvant therapy (TNT), involving giving both radiation and full systemic chemotherapy before surgery, and two trials explored giving neoadjuvant chemotherapy (nCT) alone.

Quality of evidence

The review identified ten phase II-III randomised control trials totalling 5,157 patients with locally advanced operable rectal cancer from 2015 – 2023 (see Table 1). The trials themselves were heterogeneous in their study design; with four trials comparing Consolidation TNT with long-course chemoradiotherapy (LCRT), two trials comparing Induction TNT with LCRT, two trials comparing Induction TNT with Consolidation TNT, and two trials comparing nCT with LCRT.

Studies were conducted in Poland, Korea, Germany, France, Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, China, Canada, Switzerland, and the United States across a total of 446 centres, thus the patients in the studies similar to our target population for this guideline. One point to note is that most studies limited

participants to those with ECOG/WHO scores of between 0 and 2. This may represent an important differences between trial participants and patient populations with the disease.

Patient Eligibility

Patients eligible for treatment of rectal cancer based on the described criteria include those with locally advanced operable disease. Key eligibility criteria across various trials include:

1. **Tumour Characteristics**: T, N, M status and tumour location (as listed in Table 1)
2. **Radiological imaging findings:** Baseline imaging, using a combination of computed tomography CT, MRI and EUS (endoscopic ultrasound) confirms local tumour characteristics (e.g. distance from the anal verge and involvement of surrounding structures) and presence of metastases
3. **Clinico-pathological risk factors:** involvement of tumour in surrounding structures
4. **Patient factors**: Patients comorbidities, performance status scores, or age
5. **Patient preferences**
6. **Treatment goals**

Table 1: Summary of Patient Eligibility criteria in trials

Trial Name	Pt in Study	T	N	M	Location	MRF	EMVI	Levator, intersphincteric space involvement	Positive / Enlarged lateral lymph node
PROSPECT	n=1,128	cT2	N+	M0	-	-	-	-	-
		cT3	N any	M0	-	-	-	-	-
CONVERT	n=663	cT2	N+	M0	<=12cm from anal verge	N	-	-	-
		cT3-4	N any	M0	<=12cm from anal verge	N	-	-	-
STELLAR	n=599	cT3-4	N any	M0	distal or middle third	-	-	-	-
OPRA	n=324	cT3-4	N0	M0	-	-	-	-	-
		cT any	N1-2	M0	-	-	-	-	-

Trial Name	Pt in Study	T	N	M	Location	MRF	EMVI	Levator, intersphincteric space involvement	Positive / Enlarged lateral lymph node
RAPIDO	n=912	T4a	N any	M0	<16cm from anal verge	-	-	-	-
		T4a	N any	M0	<16cm from anal verge	-	-	-	-
		T any	N2	M0	<16cm from anal verge	-	-	-	-
		T any	N any	M0	<16cm from anal verge	Y	Y	-	Y
PRODIGE 23	n=461	cT3-4	N any	M0	<15cm from anal verge	-	-	-	-
CAO/ARO/AIO-12	n=311	cT3	N any	M0	<6cm from anal verge	-	-	-	-
		>cT3b	N any	M0	>= 6 to 12 cm	Y	-	-	-
		cT4	N any	M0	<=12cm from anal verge	-	-	-	-
		cT any	N+	M0	<=12cm from anal verge	-	-	-	Y
KCSG CO 14-03	n=110	cT3-4	N any	M0	<=12cm from anal verge				
POLISH II	n=541	cT3-4	N any	M0	-				
GCR-3	n=108	cT3-4	N any	M0	<=12cm from anal verge				
		cT any	N=	M0	<=12cm from anal verge				

Results of studies by type of neoadjuvant intervention

Neoadjuvant Chemotherapy

Two randomised trials assessed the omission of radiotherapy in the neoadjuvant setting (Mei et al., 2023 - CONVERT, Schrag et al., 2023 - PROSPECT). The results of the PROSPECT study found that selective use of chemoradiotherapy was found to be non-inferior to chemoradiotherapy with respect to disease-free survival and overall survival. The CONVERT study reported on pathological complete response and found similar rates in patients undergoing neoadjuvant chemotherapy with CAPOX versus chemoradiation.

Consolidation Total Neoadjuvant Therapy

Four randomised trials evaluated the efficacy of consolidation Total Neoadjuvant Therapy (Jin et al., 2022 - STELLAR, Bahadoer et al., 2021 - RAPDO, Kim et al., 2018- KCSG CO 14-03, Bujko et al., 2004 - POLISH II). Three trials, STELLAR, RAPIDO, and POLISH II, provide insight into the efficacy of consolidation TNT compared with chemoradiotherapy (CRT) in terms of disease free survival (DFS). TNT shows comparable or better DFS compared to CRT, with RAPIDO demonstrating a significant reduction in disease-related treatment failures. TNT appeared to improve OS in the STELLAR and POLISH II trials, while RAPIDO shows no significant difference. TNT significantly improved ypCR rates in STELLAR and RAPIDO, while KCSG CO 14-03 and POLISH II show non-significant trends favouring TNT.

Induction Total Neoadjuvant Therapy

Two randomised trials evaluated the efficacy of induction Total Neoadjuvant Therapy (Conroy et al., 2021 - PRODIGE-23, Fernandez-Martos et al., 2015 - GCR-3). The PRODIGE-23 trial shows a significant improvement in DFS with TNT, whereas the GCR-3 trial indicates no significant difference between TNT and CRT. The PRODIGE-23 trial suggests a trend towards improved OS with TNT, although the difference is not statistically significant. The GCR-3 trial also shows no significant difference in OS between TNT and CRT. The PRODIGE-23 trial demonstrates a significantly higher ypCR rate with TNT compared to standard care, highlighting a potential advantage of TNT in achieving better tumor eradication.

Induction vs Consolidation Total Neoadjuvant Therapy

Two randomised trials evaluated the differences between consolidation and induction neoadjuvant chemotherapy (Garcia-Aguilar et al., 2022 - OPRA, Fokas et al., 2019 - CAO/ARO/AIO-12). The OPRA trial indicated similar 3-year DFS rates for both induction (INCT-CRT) and consolidation (CRT-CNCT) approaches, with neither showing superiority over the historical control. The CAO/ARO/AIO-12 trial shows higher ypCR rates in the consolidation group (CRT-CNCT) compared to the

induction group (INCT-CRT), with the consolidation group meeting the predefined statistical hypothesis for improved ypCR. The OPRA trial suggests a higher TME-free survival in the consolidation group (CRT-CNCT) compared to the induction group (INCT-CRT). These findings suggest that while DFS is comparable between the two approaches, consolidation TNT may offer advantages in achieving higher ypCR rates and better TME-free survival, making it a potentially more effective strategy for non-operative management.

Benefits and Harms

The potential benefits of neoadjuvant therapy in rectal cancer may be divided into two main clinical achievements: improvement of survival characteristics, and increase of local control possibly enabling non-operative management. Neoadjuvant chemotherapy may give enhanced systemic disease control, and better treatment adherence.

The most recent neoadjuvant treatments in locally advanced rectal cancer summarised in this document (i.e. TNT/nCT) offer several potential benefits and harms:

Benefits:

1. **Increased likelihood of complete response:** TNT/nCT may increase the likelihood of achieving a complete response, where the tumour shrinks significantly or disappears entirely. This can potentially make surgery more effective and less invasive.
2. **Improved downstaging:** Preoperative therapy may shrink the tumour and decrease the stage of the cancer, making it easier to remove surgically and potentially reducing the need for extensive surgery or permanent colostomy.
3. **Enhanced local control:** By treating the tumour with chemotherapy before surgery, neoadjuvant chemotherapy may improve local control by reducing the risk of local recurrence.
4. **Potential for organ preservation:** In some cases, successful TNT/nCT may allow for organ preservation by enabling less invasive surgical techniques, such as sphincter-sparing surgery, which preserves bowel function.

Harms:

1. **Increased toxicity:** Combining chemotherapy and radiation therapy before surgery may increase treatment-related toxicity, leading to side effects such as fatigue, gastrointestinal symptoms (nausea, diarrhoea), skin reactions, and hematologic toxicity.
2. **Delayed surgery:** Neoadjuvant therapy may delay the timing of surgery, which could potentially allow the tumour to progress or metastasize during the waiting period.

3. **Potential for over-treatment:** Some patients may receive neoadjuvant therapy unnecessarily if their tumours could have been effectively treated with surgery alone. This exposes them to the risks of chemotherapy and/or radiation without additional benefit. This is of particular risk for the nCT cohort, where chemotherapy can be followed by radiation if the chemotherapy alone does not result in sufficient size reduction of tumour.
4. **Risk of incomplete response:** Not all patients will respond favourably to neoadjuvant therapy, and some may experience disease progression or metastasis despite treatment.
5. **Surgical Complications:** Surgical removal can still carry risks of complications such as bleeding, infection, and damage to nearby structures.

In summary, TNT/nCT in locally advanced rectal cancer offers the potential for improved outcomes, including increased rates of complete response, enhanced local control, and potential for organ preservation. However, it also comes with risks, including increased treatment toxicity, potential delays in surgery, and the possibility of incomplete response or over-treatment. The decision to pursue TNT/nCT should be made on a case-by-case basis, considering the individual patient's tumour characteristics, overall health, and treatment goals.

Preferences and values

Rectal cancer patient preferences and values regarding neoadjuvant therapy are individualised. Patients prioritise knowledge and understanding the available treatment options, particularly the balance between treatment toxicities and long-term outcomes.

Recognising that each patient's experience with cancer and treatment is unique, preferences can vary widely based on factors such as personal health goals, lifestyle considerations, and tolerance for side effects. Patients need reassurance that tumour conferences are in a position to consider the best possible evidence-based treatment for the individual patient.

Given the non-inferiority of total neoadjuvant therapy/ neoadjuvant chemotherapy in locally advanced rectal cancer when compared with chemoradiotherapy, patient preference is of particular importance when deciding on a treatment. Individual patient goals (e.g. organ preservation) and the potential impact of toxicities associated with these rectal cancer treatments should contribute to the treatment selection decision.

Ongoing patient education and open communication play crucial roles in ensuring that patients are well-informed participants in shared decision-making processes. Empowering patients with knowledge about treatment options, potential risks, and benefits allows them to make choices aligned with their values and preferences, ultimately fostering a sense of agency and autonomy in their cancer journey. This

communication and education should be ongoing, i.e. not limited to the initial consultation/s but available at a variety of times.

Patients are often exposed to numerous options and an excess of information (e.g. through conversations or health information seeking outside of consultations with their medical team). Building trust in the medical team as the primary and most reliable source of information on the treatment will reassure patients that all options are being considered. Adequate time for communication with patients to ensure their understanding of their options is also essential. It could therefore be beneficial to have different team members available to answer patient questions over multiple sessions, as it is very difficult for patients to absorb all relevant information and consider all of their questions in a single consultation. Face-to-face discussions and communication of health information by the team are vital, particularly given the individualised nature of treatment options.

Issues around quality of life should also be addressed with the patient. While oncological control is of utmost importance, patients should be reassured that other issues arising from their disease and treatment (e.g. neuropathy, neutropenia, anaemia, fatigue, bowel function, sexual function) are also a priority and receive support and potential toxicities should be part of the communication. Likewise, specific factors with rectal cancer treatment relating to patient characteristics (e.g. sex, age, etc.) should be communicated.

Resources, capacity, equity and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

The following resources, capacity and other considerations were discussed by the Guideline Development Group:

Time to surgery

The use of TNT/nCT may result in surgery occurring later in the treatment pathway. This may impact the key performance indicators monitored by the NCCP. The duration of TNT/nCT treatment can be predicted and timelines set accurately therefore once surgeons are informed of timelines there are no substantial issues with scheduling foreseen.

Increase in non-operative management

These recommendations are not intended to address a non-operative approach however the guideline development group recognise that there may be down-stream radiological and endoscopic resource implications of TNT/nCT treatment as in some cases a non-operative approach may be possible.

Recommendation 2.1.1

All patients diagnosed with locally advanced operable rectal cancer should be considered for neoadjuvant therapy. The optimal type of neoadjuvant therapy should be discussed at a tumour conference.

The following criteria should be considered when choosing a treatment option:

- Tumour location
- Radiological findings
- Clinico-pathological risk factors
- Patient factors (e.g. comorbidities, age)
- Patient preferences
- Treatment goals

Quality of Evidence: High **Grade of recommendation: Strong**

Good practice point

- The approach to neoadjuvant therapy should be individualised, treatment decision should be based on the tumour conference recommendation and patient factors including patient preferences.
- In some patients neoadjuvant therapy may result in a complete clinical response and a non-operative management approach may be possible.

Practical consideration for patient care

- Patients should be offered more than one opportunity to discuss their treatment and potential side effects, and should be given the opportunity to ask any questions.
- These discussions can be with different members of the MDT for example a Consultant, an Advanced Nurse Practitioner, or a Clinical Nurse Specialist.

3 Methodology

3.1 List of clinical questions

Clinical question (code: Rectal_Neo_1)

In patients diagnosed with locally advanced operable rectal cancer, are there subgroups of patients that should be considered for neoadjuvant therapy?

Population	Patients diagnosed with locally advanced operable rectal cancer

Intervention	Need for preoperative therapy indicated by any of the following:
	• Prognostic indicators based on MRI:
	  ○ standard TNM staging
	  ○ tumour location
	  ○ CRM/mesorectal fascia (MRF) status
	  ○ radiological extramural vascular invasion (EMVI) status
	• Endorectal ultrasound
	• Endoscopy
	• Surgical concern over ability to sphincter spare
	• MMR status
	Other patient specific factors

Control	-
Outcome	Overall survival Disease-free survival Recurrence Incidence of Distant Metastases Pathological complete response (ypCR) Duration of Neoadjuvant Treatment Safety and Toxicity Quality of Life Organ preservation Clinical response - Improved patient compliance

3.2 Describe and document the evidence search

The clinical question outlined above was used to conduct a literature search of primary literature. A systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP and is available upon request. The literature search strategies for each key question are available upon request.

3.3 Describe the method of screening and evidence appraisal

An evidence methodologist and two research officers screened the literature searches independently to identify relevant primary papers. Any disagreements on primary paper inclusion were agreed through discussion.

All included primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

There were three main points considered when appraising the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of the guideline? (external validity)

3.4 Resource implications

Any potential barriers or resource implications of implementing the recommendations were identified by the guideline development group during meetings to discuss and agree the clinical recommendations. These are documented under 'Resources, capacity, equity and other considerations' for each clinical question in Section 4 National Clinical Guideline.

3.5 Consultation

National review

The draft guideline was signed-off by the GDG before going to national stakeholder review.

It was placed on the NCCP website and circulated to relevant organisations and individuals for comment between XXXX and XXX 2024.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided along with a completed conflict of interest form.

International review

The draft guideline was also submitted for international expert review. The GDG nominated the following experts to provide feedback on the draft guideline:

- XXXXXX
- XXXXXX

The reviewers were chosen by the GDG based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the National Review.

All feedback received was reviewed by the GDG. Suggested amendments and supporting evidence were reviewed and consensus reached to accept or reject the amendments. All modifications were documented and the report is available upon request.

3.6 National implementation plan

An implementation plan was developed based on the NCEC Implementation guide (DoH, 2018). It outlines the actions required to implement each recommendation, who has lead responsibility for delivering the action, the timeframe for completion and the expected outcomes of implementation (see Appendix III National Implementation Plan).

This National Clinical Guideline including the implementation plan should be reviewed by the multidisciplinary team and senior management in the cancer centre/hospital as it outlines the actions required to implement the recommendations.

The CEO, General Manager and Clinical Director of each cancer centre/hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline.

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document.

3.7 Governance and approval

The guideline was submitted to the NCCP Executive Management Team on the dd/mm/yyyy for approval.

A full list of the members can be found in Appendix II: Membership of NCCP Executive.

3.8 Communication and dissemination plan

This National Clinical Guideline is available on the HSE National Central Repository.

A Communication and Dissemination Plan was developed by the GDG to raise awareness of the development of this guideline, to ensure effective communication and collaboration with all key stakeholders throughout the various stages of guideline development process and to maintain momentum for the widespread adoption of the guideline.

In conjunction with the HSE Communications Division, key stakeholders were identified and a list of strategies was developed to inform them of the new guideline

(see Appendix IV: Communication and Dissemination Plan). The implementation of the guideline will also be supported by communication, training and education.

3.9 Sustainability

Plan for national monitoring and audit

3.9.1.1 Monitoring

Each cancer centre/hospital should implement a systematic process of gathering information and tracking over time to achieve the objectives of this guideline.

The Colorectal Tumour Conference in each cancer centre/hospital should monitor the implementation of recommendations specific to their practice.

3.9.1.2 Audit

It is important that implementation of this National Clinical Guideline is audited to ensure that this guideline positively impacts patient care. Each cancer centre/hospital should audit implementation of this guideline at least annually.

National audit tool

A National Audit Tool has been developed for this guideline (Appendix V: National Audit Tool), which can be used by cancer centres/hospitals to audit their compliance with the recommendations in this guideline.

It is intended that this audit tool will provide each Colorectal Cancer Tumour Conference with a baseline tool through which they can identify areas that require improvements. Users of this audit tool are free to add in additional statements, as they deem appropriate and adopt this tool for use in their own setting. This audit tool is to be used to retrospectively audit processes and the presented audit statements are examples to support audit.

3.10 Review/update

This guideline was issued in dd/mm/yyyy and will be considered for review by the NCCP in three years.

Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be noted in the guidelines section of the NCCP websites.

4 Abbreviations

CRM - Circumferential Resection Margin

DFS - Disease-Free Survival

EMVI - Extramural Vascular Invasion

ERUS - Endorectal ultrasound

GRADE - Grading of Recommendations Assessment Development and Evaluation

HSE - Health Service Executive

MDT - Multidisciplinary Team

MRI - Magnetic Resonance Imaging

nCT - Neoadjuvant Chemotherapy

NCCP - National Cancer Control Programme

NCEC - National Clinical Effectiveness Committee

OS - Overall Survival

QoL - Quality of Life

TNT - Total Neoadjuvant Therapy

ypCR - Pathological Complete Response

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5 Glossary of Terms

Adjuvant Systemic Chemotherapy
Adjuvant systemic chemotherapy refers to the use of anticancer drugs administered after the primary treatment, typically surgery, to eliminate any remaining cancer cells and reduce the risk of cancer recurrence. These drugs travel through the bloodstream to reach and treat cells all over the body.

Benefits and Harms
Benefits refer to improved quality of life and reductions in mortality and morbidity. There are physical risks of harm such as exposure to radiation and there are also emotional and psychological risks of harm such as anxiety and depression.

Chemoradiotherapy
Chemoradiotherapy, also known as chemoradiation, is a treatment that combines chemotherapy and radiation therapy to increase the effectiveness of cancer treatment. Chemotherapy involves the use of drugs to destroy cancer cells, while radiation therapy uses high-energy radiation to target and kill cancer cells. This combined approach can enhance the sensitivity of cancer cells to radiation, improving the overall treatment outcome by reducing the size of tumours, preventing recurrence, and sometimes enabling more successful surgical removal of the cancer.

Circumferential Resection Margin (CRM)
The CRM is the distance in millimetres between the deepest point of tumour invasion and the edge of the resected tissue. A positive CRM, where cancer cells are present at the margin, indicates a higher risk of recurrence and worse prognosis. Conversely, a negative CRM, where there is a clear margin around the tumour, is associated with better outcomes.

Confidence intervals
Confidence intervals indicate the consistency, or variability of a result. If a study has 95% confidence interval calculated, this means that if the study was repeated multiple times with samples from the whole population and the confidence intervals were calculated for each of those repeated studies, then the true value would lie within the calculated confidence intervals 95% of the time.

Consolidation Total Neoadjuvant Therapy
Consolidation Total Neoadjuvant Therapy involves systemic chemotherapy after radiation therapy.

Disease-Free Survival (DFS)
Disease-free survival (DFS) refers to the length of time after primary treatment for cancer ends that a patient survives without any signs or symptoms of that cancer.

Measuring DFS in clinical trials helps evaluate how well a new treatment works by determining the period during which patients remain free from the disease after treatment.

Endorectal Ultrasound
Endorectal ultrasound (ERUS) is a procedure in which a probe that sends out high-energy sound waves is inserted into the rectum. The sound waves bounce off internal tissues and organs, creating echoes that form a picture called a sonogram. This imaging technique is used to look for abnormalities in the rectum and nearby structures, including the prostate, aiding in the diagnosis and staging of rectal and other nearby cancers.

Endoscopy
Endoscopy is a medical procedure that uses an endoscope to examine the interior of a body. An endoscope is a thin, tube-like instrument equipped with a light and a lens for viewing. It may also have a tool to remove tissue for further examination under a microscope. This procedure allows doctors to inspect and diagnose conditions within the body without making large incisions.

Good practice points
Good practice points are based on the clinical expertise of the Guideline Development Group.

Hazard ratio
A measure of how often a particular event happens in one group compared to how often it happens in another group, over time.

Induction Total Neoadjuvant Therapy
Induction Total Neoadjuvant Therapy involves systemic chemotherapy before radiation therapy.

Locally Advanced Rectal Cancer
Locally advanced rectal cancer refers to cancer that has spread from the rectum to nearby tissues or lymph nodes, but not to distant parts of the body. Typically, this includes stages II and III of rectal cancer, where the tumour has invaded through the rectal wall and may involve adjacent organs or regional lymph nodes.

Neoadjuvant Chemotherapy (nCT)
Neoadjuvant chemotherapy refers to the administration of chemotherapy before the primary treatment, typically surgery, to shrink a tumour. This approach aims to make the tumour easier to remove and to increase the chances of successful surgery. It is commonly used in the treatment of various cancers, including breast, rectal, and cervical cancers. Neoadjuvant chemotherapy can help in reducing the tumour size,

managing locally advanced disease, and improving surgical outcomes by making inoperable tumours operable.

Neoadjuvant Therapy
Neoadjuvant therapy is a treatment given as a first step to shrink a tumour before the main treatment, which is usually surgery. This therapy includes various methods such as chemotherapy, radiation therapy, and hormone therapy. The goal of neoadjuvant therapy is to reduce the size of the tumour, making it easier to remove surgically and to improve the overall outcome of the treatment by potentially increasing the chances of a complete surgical resection and reducing the risk of cancer recurrence.

Odds ratio
An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Odds ratio can be expressed as <1 indicating that the intervention group had more favourable outcome than the control group, >1 indicating worse outcome for the intervention group, and 1 indicating no difference between groups.

Oncological Control
Oncological control refers to the management and containment of cancer within the body. It involves strategies and treatments aimed at preventing the growth and spread of cancer cells, ensuring that the disease does not progress or recur. Oncological control can include a variety of approaches such as surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy. The goal is to achieve remission, maintain the stability of the disease, and improve the patient's quality of life.

Overall Survival (OS)
Overall survival (OS) is defined as the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. It is a crucial measure used in clinical trials to assess the efficacy of a new treatment. The calculation of overall survival does not take into account the cause of death; it simply measures the time a patient lives after diagnosis or initiation of treatment regardless of whether the death was due to cancer or another cause.

Pathological Complete Response (ypCR)
Pathologic complete response (ypCR) refers to the absence of all signs of cancer in tissue samples removed during surgery or biopsy after treatment with radiation or chemotherapy. To determine ypCR, a pathologist examines the tissue samples under a microscope to check for the presence of cancer cells. This response is an

important indicator of the effectiveness of the treatment and is used to assess the likelihood of long-term cancer control.

p-value

The p-value is related to the significance level. If the critical alpha value is 0.05, then the p-value must be smaller than 0.05 for the test to have a statistically significant result. If the p-value is greater than the critical alpha value, then the test does not have a statistically significant result.

Phase II-III Randomised Control Trials

Phase II-III randomized control trials are studies that test how well new treatments work for a certain type of cancer or disease and compare the new treatment with a standard treatment. Phase II trials focus on the efficacy and side effects of a new treatment in a larger group of people than Phase I trials. They aim to determine if the treatment works against the cancer by shrinking tumours or slowing their growth. Phase III trials involve even larger groups and compare the new treatment directly with the current standard treatment to determine which is more effective and has fewer side effects. These trials often involve random assignment of participants to different treatment groups to ensure unbiased results.

Preoperative Radiotherapy

Preoperative radiotherapy refers to the administration of radiation therapy before Preoperative radiotherapy refers to the administration of radiation therapy before surgical intervention. This treatment is used primarily to reduce the size of a tumour, making it easier to remove and potentially increasing the likelihood of a successful surgery. It is commonly applied in cases of rectal, lung, and soft tissue cancers.

Preferences and values

The patient preferences and values statements were developed by the multidisciplinary Guideline Development Group including patient representatives. Patient members were given priority during guideline meetings to discuss preferences and values.

The Guideline Development Group tried to identify what an informed patient and their families would prefer. The value statements refer to what the Guideline Development Group believe are the values that are driving patient and family preferences.

Practical considerations regarding patient care

These are statements developed with the patient Guideline Development Group members on issues that were important to them with regards to their own experience of the diagnosis and staging of their cancer.

Prognostic Indicators

Prognostic indicators are factors or conditions that can be used to estimate the likely

outcome of a disease, such as cancer. These indicators help predict the chance of recovery, the likelihood of disease recurrence, and overall survival rates. Examples of prognostic indicators include the cancer's stage, tumour size, histological grade, genetic mutations, hormone receptor status, and the patient's overall health and response to treatment.

Radiological Imaging

Radiological imaging involves various techniques to create detailed pictures of the inside of the body. These methods use different forms of energy, such as x-rays, ultrasound, radio waves, and radioactive substances. Radiological imaging is essential for diagnosing diseases, planning treatments, and monitoring the effectiveness of therapies.

Relative risk

A measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group. A relative risk of 1 means there is no difference between two groups in terms of their risk of cancer, based on whether

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6 Appendix

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Appendix I Members of the Guideline Development Group

A conflict of interest form was signed by all members of the GDG. No conflicts of interest were declared.

Name	Title/position	Role on guideline group
Chairs of the Guideline Development Group		
Prof Paul McCormick	Consultant Colorectal Surgeon	Co-chair, writing member
Dr Eve O'Toole	Head of Evidence & Quality Hub, NCCP	Co-chair, writing member
Patient representatives		
Mr Frank Twomey	Patient/Service User Partner	Writing member
Mr John O'Connell	Patient/Service User Partner	Writing member
Medical Oncology		
Dr Darren Cowzer	Consultant Medical Oncologist, The Mater Misericordiae University Hospital	Writing member
Dr Derek Power	Consultant Medical Oncologist, Cork University Hospital	Writing member
Dr Brian Bird	Consultant Medical Oncologist, Bons Secours Cork	Writing member
Dr Greg Leonard	Consultant Medical Oncologist, University Hospital Galway	Writing member
Radiation Oncology		
Dr John Gaffney	Consultant Radiation Oncologist, University Hospital Galway	Writing member
Prof Daniel Cagney	Consultant Radiation Oncologist, Mater Private Network	Writing member
Surgery		
Prof Fiachra Cooke	Consultant Colorectal Surgeon & Lead Clinician South East Rectal Cancer Programme, University Hospital Galway	Writing member
Prof Paul McCormick	Consultant Colorectal Surgeon, St. James's Hospital	Writing member
Pathology		
Prof Kieran Sheahan	Consultant Pathologist, St. Vincent's University Hospital	Writing member
Radiology		
Prof. Martina Morrin	Consultant Radiologist, Beaumont Hospital	Writing member

Dr Aileen O'Shea	Consultant Radiologist Beaumont Hospital	Writing member
Dr Alison Corr	Consultant Radiologist, St James Hospital	Writing member
Nursing		
Ms Katrina O Connor	Cancer Nurse Coordinator, St. James's Hospital	Contributor
Ms Vivienne Curran	Colorectal Nurse Specialist, Mercy Hospital	Writing member
Ms Emma McNamara	Colorectal Surgical Cancer Coordinator, Limerick University Hospital	Contributor
Library		
Mr Gethin White	Librarian, HSE	Contributor
NCCP		
Dr Eve O'Toole	Head of Evidence and Quality Hub, NCCP	Writing member
Ms Louise Murphy	Senior Research Officer, NCCP	Writing member
Ms Nerissa Keating	General Manager, Strategy, NCCP	Writing member
Ms Patricia Heckmann	Assistant National Director, Systemic Therapy Programme, NCCP	Contributor
Mr Peter Dennan	Clerical Officer, NCCP	Administrative support
Mr Paul Flood	Research Officer, NCCP	Writing member

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Appendix II Membership of NCCP Executive

Name	Role and position

Sign-off by Chair of Approval Governance Group

National Clinical Guideline: *Neoadjuvant treatment of patients with locally advanced rectal cancer* was formally ratified and recorded in the minutes of the Approval Governance Group on dd/mm/yyyy.

Name: (print)	
Title:	
Signature: **(e-signatures accepted)**	

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Appendix III National Implementation Plan

National Clinical Guideline: Diagnosis and staging of patients with locally advanced rectal cancer
Date National Clinical Guideline approved: dd/mm/yyyy
Expected date of full implementation: dd/mm/yyyy
Lead responsibility for national implementation:

Implementation action	Implementation barriers / enablers	List of tasks to implement the action	Lead responsibility for delivery of the action	Expected completion date	Expected outcomes
Develop a communication and dissemination plan to ensure that cancer centres are aware of guideline recommendations.	Enablers: Assistance of HSE Communications and HSE Digital Potential Barriers: Professional-patient interaction given complex nature of treatment. Patient perceptions and treatment preferences.	Please see Appendix IV Communication and Dissemination Plan	NCCP	Following guideline publication	Increased awareness of National Clinical Guideline recommendations.
Communicate potential impact of clinical recommendation on KPIs to NCCP Cancer Intelligence Team.	Enablers: NCCP Cancer Intelligence Team	Communicate with Cancer Intelligence Team, NCCP	NCCP	Prior to guideline publication	Accurate interpretation of key performance indicator data

Appendix IV Communication and Dissemination Plan

Key stakeholders were identified by the GDG and in conjunction with the HSE Communications Division, a list of strategies was developed to inform these stakeholders of the new guideline. Some strategies will include:

- Official publication and launch of the guideline.
- Direct communication from NCCP Director to hospital and cancer network managers raising awareness and setting out expectations/actions.
- Circulation to the networks who participated in developing and reviewing the guideline.
- Circulation to NCCP staff.
- Liaison with HSE Clinical Programmes, academic faculties and professional bodies for dissemination to their members.
- Liaison with the Irish Cancer Society and relevant voluntary organisations and patient advocacy groups to ensure guidelines are represented in their patient and public information.
- Promotion through the HSE/NCCP website, internal HSE media, social and print media.
- NCCP to include details of the guideline in presentations by clinical leads, sub-group chairs, NCCP Director.
- NCCP to promote the guideline at conferences, workshops, and CPD sessions.

A plain language summary of the guideline will be included as a key element of the Communication and Dissemination Plan - for patients, their families and other non-specialists who may be interested in the potential implications of the recommendations within the guideline and what it may mean for them.

Description of stakeholder communications	Communication method	Owner	Timeline
Patients			
Plain language summary	Guideline	Project team	Pre 'go live'
Guideline Development Group			
New guideline alert	Email	Project team	Pre 'go live'
National stakeholders			
New guideline to Hospital Managers/Cancer Network Managers	Email	National Director, NCCP	Pre 'go live'
New guideline to relevant stakeholders (incl. National groups, organisations,	Email	Project team	Pre 'go live'

faculties, patient support & advocacy groups, international reviewers)			
New guideline to NCCP staff	Email	Project team	Pre ‘go live’
Press Release (HSE website)	Article	Project team/HSE Comms	‘go live’
HSE All Staff Update via Health Service News	Email	Project team/HSE Comms	Within 2 weeks of 'go live'
Health Matters article	Article	Project team/Health Matters	Within 2 months of 'go live'
Medical Independent article	Article	Project team/Medical Independent	Within 2 months of 'go live'

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Appendix V National Audit Tool

Objective of Audit Tool

National procedures and guidance on how to conduct a clinical audit are available from HIQA (2023) and the HSE (2023).

Each statement in this audit tool has been taken from the accompanying 'National Clinical Guideline: Diagnosis and staging of patients with locally advanced rectal cancer' focusing on developments in practice.

Each cancer centre/hospital can assess to what degree they comply with the statements within their own rectal cancer tumour conference.

It is intended that this audit tool will provide each cancer centre with a baseline tool through which they can assess their own practice and identify areas which require improvements.

Users of this audit tool are free to add in additional statements, as they deem appropriate and adopt this tool for use in their own setting. This audit tool is to be used to retrospectively audit practices and the presented audit statements are examples to support audit.

Methodology

Population:	Patients with rectal cancer
Sampling:	A total of 20% or 20 patients, whichever is greater, should be selected
Frequency:	At least annually
Method:	Record **Y** for **Yes**, if the criteria are met. Record **N** for **No**, if criteria are not met. Record **N/A** for **Not applicable**.
Calculation of Compliance Rate %:	The score, expressed as a percentage, is calculated by dividing the number of "yes" and "no" answers. "Not applicable" answers are excluded from the calculation of the percentage score. **Example:** If there are 6 "yes" and 2 "no" answers, the score is calculated as follows:

	6 (yes answers) divided by 8 (total of yes and no answers) multiplied by 100 = 75%

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Audit Topic and Title:				
Hospital:	[Name]			
Audit lead by:	[Name and title]			
Date of audit:	[dd/mm/yyyy]			
Evidence source:				
Is standard/criteria being met for the following statements: **Compliance requirement**	**Yes**	**No**	**N/A**	**Compliance Rate**
Statement 1 (Recommendation 2.1.1) For patients with operable locally advanced rectal cancer, neoadjuvant therapy has been considered at tumour conference.				

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Appendix VI Plain Language Summary

Summary of National Clinical Guideline

If you have rectal cancer that can be treated with surgery, you should talk to your doctor about treatments to have before the surgery. These treatments include chemotherapy (cancer drugs) and radiation. A team of cancer experts will recommend the best treatment plan and discuss it with you. In the end, you will decide which treatment you want.

Who is this for?

This recommendation is for you if:

- You have been diagnosed with rectal cancer that can be removed with surgery.
- Your cancer is considered locally advanced, meaning it has spread nearby but not to distant parts of your body.

Things to Consider When Choosing a Treatment

When deciding on the best treatment option for you, your healthcare team will look at:

- Where the tumour is located in your rectum.
- What tests show about your tumour.
- Your overall health and any other medical conditions you may have.
- Your age.
- What you prefer and feel comfortable with.
- The goals of the treatment, such as shrinking the tumour to make surgery easier or to reduce the risk of the cancer coming back.

What does this mean for you?

Questions you may want to ask your healthcare professionals?

- What are my options for treatment?
- How long will the treatment take?

- Will there be side-effects?
- Will this impact my day to day life?
- Can I continue to work
- Who do I contact if something doesn't feel right or I am feeling unwell?
- What happens next?

Understanding the language

Medical Term	Plain language explanation
MRI	An imaging scan that uses magnets and radio waves to take detailed pictures (2D/3D) of the body's organs, muscles, soft tissues, and structures. It does not use radiation. It is sometimes used to clarify queries on other scan.
Staging	An assessment of the size of your cancer and whether it has spread to other parts of the body. This assessment helps your doctor decide the best treatment for you.
Distant metastasis	Cancer that has spread to other parts of the body.

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Appendix VII Grading the recommendations in this guideline

The Guideline Development Group assigned each recommendation a quality of evidence and grade of recommendation. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides an explicit system for rating the quality of evidence and whether the recommendation is strong or weak (Guyatt et al., 2008).

Quality of evidence

It is recognised that in guideline development that just assessing the level of evidence does not take into account the methodological quality of each individual study or the quality of the body of evidence as a whole (Harbour and Miller, 2001). The Guideline Development Group used an amended GRADE system which considers the following factors when classifying the quality of evidence; high, moderate or low (Guyatt et al., 2008):

- Study design
- Study design limitations
- Consistency of results
- Directness of the evidence
- Imprecision of results
- Reporting bias

Table 2: Quality of evidence adapted from GRADE working group 2013

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Grade of recommendation

There are two grades of recommendation: strong or weak. These reflects the balance of the following items:

- The quality of the body of evidence
- The balance between benefit and harm to patient

- Patient preferences and values
- Resources/cost

Table 3: Grade of recommendation adapted from GRADE working group 2013

Strong	A strong recommendation is one for which the Guideline Development Group is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). Strong recommendations are not necessarily high priority recommendations. A strong recommendation implies that most or all individuals will be best served by the recommended course of action.
Weak	A weak recommendation is one for which the desirable effects probably outweighs the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's circumstances, preferences, and values. When there are weak recommendations caregivers need to allocate more time to shared decision-making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.

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