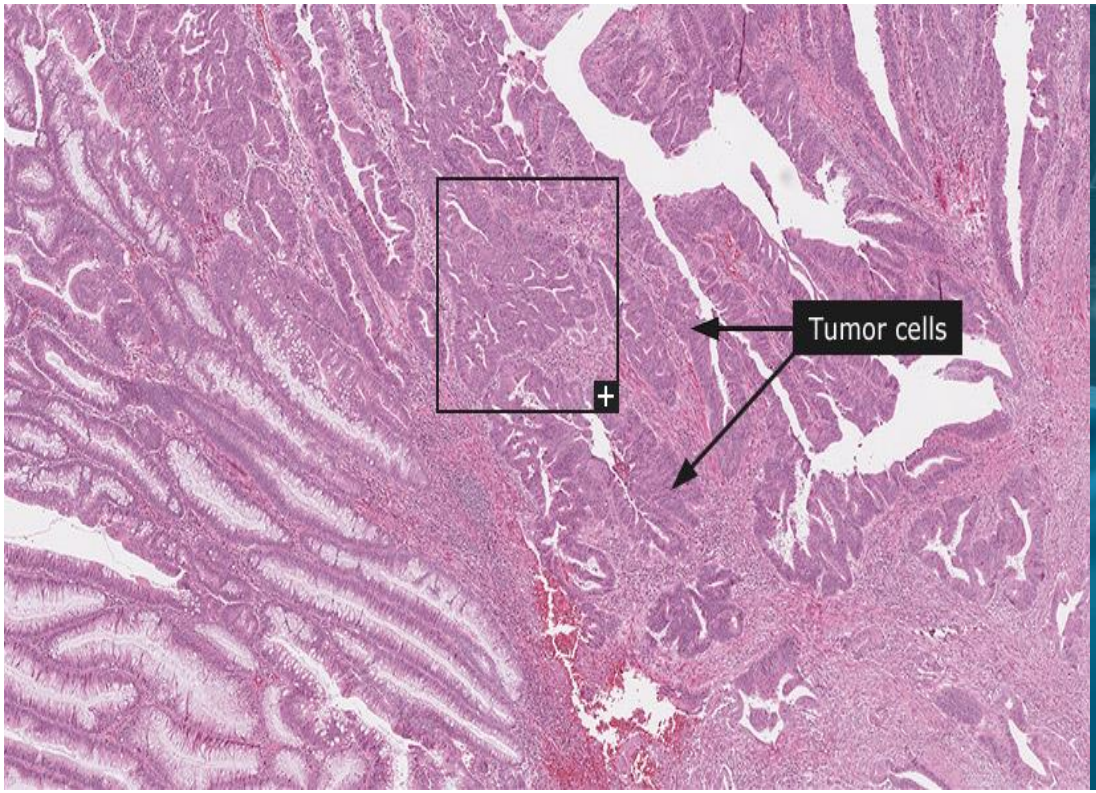
KCE REPORT 260

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART: 1 INTRODUCTION AND METHODOLOGY



KCE REPORT 260
GOOD CLINICAL PRACTICE

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Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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ABBREVIATIONS

ABBREVIATION	DEFINITION
AHRQ	Agency for Healthcare Research and Quality
AR	Abdominal resection
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
ELRR	Endoluminal locoregional resection
EMVI	Extramural venous invasion
ERUS	Endorectal ultrasound
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
FU	Fluorouracil
GDG	Guideline Development Group
GIN	Guidelines International Network
HR	Hazard ratios
IKNL	Integraal Kankercentrum Nederland
KCE	Belgian Health Care Knowledge Centre
LR	Local recurrence
LRFS	Local recurrence free survival
LTME	Laparoscopic total mesorectal excision
MA	Meta-analysis
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

NICE	National Institute for Health and Care Excellence
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance
OR	Odds ratio
OS	Overall survival
PET-CT	Positron emission tomography - computed tomography
PICO	Population-intervention-comparator-outcome
PROCARE	Project on Cancer of the Rectum
QoL	Quality of life
RCT	Randomised controlled trial
RQ	Research question
RR	Risk ratio
SEER	Surveillance, Epidemiology and End Results
SR	Systematic review
TAE	Transanal excision
TEM(S)	Transanal endoscopic microsurgery
TME	Total mesorectal excision

SCIENTIFIC REPORT

1 INTRODUCTION

The development of clinical care pathways is one of the main actions described in the Belgian National Cancer Plan 2008-2010 and one of the assignments of the College of Oncology. For many years the Belgian Health Care Knowledge Centre (KCE) has collaborated with the College of Oncology by providing scientific support for the development of clinical practice guidelines that can serve as a base for care pathways. This collaboration has resulted in the publication of clinical practice guidelines on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer, cervical cancer, prostate cancer, lung cancer and head & neck cancer.

1.1 Background

Rectal cancer is often discussed within the entity of colorectal cancer. Therefore separate incidence rates are not widely available. A majority of colon and rectal cancers are adenocarcinomas (98%). Rectal cancers include some rare forms such as lymphoma (1.3%), carcinoid (0.4%), and sarcoma (0.3%).[1] In 2012 an estimated 1.4 million cases of colorectal cancer occurred worldwide. Europe includes high incidence regions.[2] The Surveilllance, Epidemiology and End Results (SEER) database reports an incidence of 42.4 per 100 000 men and women per year based on age-adjusted 2008-2012 cases and deaths. The number of deaths was 15.5 per 100 000 men and women per year during the same time period.[3] The incidence has decreased compared to earlier years (66.3 per 100 000 population in 1985) following screening and detection programs. However, colorectal cancer is still the third most common cancer in men and the second in women.[2]

The 2007 KCE guideline on rectal cancer[4] resulted in a 'Project on Cancer of the Rectum' (PROCARE) including a registry operated by the Belgian Cancer Registry for cases and quality indicators (http://procare.kankerregister.be/procare.aspx?url=Procare_statistics). PROCARE ended on December 31, 2014. For the year 2012, when the population in Belgium was 11.13 million,[5] the Belgian Cancer Registry reported 2 782 women with colon cancer, 970 women with rectal cancer and 3 075 men with colon cancer, 1 494 men with rectal cancer.[6] PROCARE feedback data from 2014 indicate a 75% accuracy of cT staging if no or short preoperative radiotherapy was given (for n=1 834). Thus 34% of cases were

under staged and 20% were over staged (http://procare.kankerregister.be/media/docs/Projecten/Procare/FB14_Annex3_TNM_general_v1.0.pdf).

1.2 The need for a guideline

The 2013 KCE report on colon cancer did not address rectal cancer. The earlier guideline on good clinical practice for rectal cancer was published in 2007,[4] followed by two reports on quality indicators in 2008[7] and 2011.[8] Since the search date of the PROCARE guideline was 2006 it was necessary to update recommendations.

1.3 Scope

A search for recent guidelines on rectal cancer was undertaken in December 2014. A search on websites from cancer institutes resulted in eight hits (see table in Appendix). A subsequent search from 2006 onwards in Ovid Medline, Embase and Cochrane database of systematic reviews yielded 361 citations (for search strategy (see table in Appendix. A first selection based on title and abstract resulted in 57 inclusions of which 28 were published after 2012. The Guideline Development Group (GDG) proposed three additional publications: one was a meta-analysis on adjuvant chemotherapy following preoperative (chemo) radiotherapy (CRT) and surgery[9] and two NCCN guidelines from 2011 and 2012. Meanwhile the NCCN guidelines have been updated to version 3.2015.[10] Guidelines were selected according to a rapid assessment based on questions 7, 8 and 10 of the AGREE II instrument (see table in Appendix) They scored positively on: the use of systematic methods to search evidence (item 7), description of the criteria for selecting evidence (item 8) and methods for formulating recommendations (item 10). After discarding duplicates and applying these inclusion criteria, 12 guidelines were selected[11-22] and their content was linked to the research questions (RQ) of the PROCARE 2007 report. Later in the process, on June 18th 2015, NCCN published a 2015 update of the guideline on rectal cancer.[23]

In order to select three RQs to update the 2007 PROCARE guideline[4] a scoping meeting was held with a large group of experts, the Scoping Group on February10th, 2015. The RQs from the 2007 PROCARE guideline were listed. If one of the selected guidelines addressed the RQs it was mentioned in the table. The Scoping Group was asked to subsequently score the RQs (see table in Appendix). The scope had to be limited to three RQs and those with the highest scores were selected after additional discussion.

1.4 Remit of the guideline

1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for three specific research questions about rectal cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The guidelines are based on clinical evidence and may not always be in line with the current criteria for National Institute for Health and Disability Insurance (NIHDI-RIZIV/INAMI) reimbursement of diagnostic and therapeutic interventions. The NIHDI may consider to review reimbursement/funding criteria based on the guidelines.

1.5 Statement of intent

Clinical guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with rectal cancer. The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.5.1 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of patients with rectal cancer, including general practitioners, oncologists, gastroenterologists, surgeons, radiologists, pathologists and nurses. It should also be of interest to patients and their families, hospital managers and policy makers.

1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the scoping, development or peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest that are available on request.

2 GENERAL METHODOLOGY

2.1 Introduction

KCE guidelines are produced according to standard principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline. At first, clinical questions were selected and the inclusion and exclusion criteria were defined in collaboration with a Scoping Group, consisting of members of the GDG and Stakeholders. The composition of the different groups is documented in the Colophon. In a second step, a literature review was conducted (including a search for recent, high quality guidelines). The third step involves formulation of recommendations based on the literature review and grading according to the GRADE approach.

2.2 The Guideline Development Group

This guideline results from collaboration between a multidisciplinary group of practising clinicians and KCE experts. Guideline development, literature review, support and facilitation were provided by the KCE Expert Team.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and Stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.3 General approach and research questions

The selection of RQs was made by the members of the GDG, representatives of professional organizations and patient representatives, constituting a Scoping Group during a meeting held at KCE on 10/02/2015. Three RQs were retained after an identification and selection process.

1. RQ1: What is the optimal staging strategy using magnetic resonance imaging (MRI)?
2. RQ2: Can local resection or transanal endoscopic microsurgical resection be performed instead of radical resection without compromising the outcome in rectal cancer patients (T1, T2)?
3. RQ3: When should adjuvant chemotherapy be considered in patients who received neoadjuvant radio(chemo)therapy?

The RQs were translated into in- and exclusion criteria using the Participants–Interventions–Comparator–Outcomes (P.I.C.O.) framework (Table 1). Patient preferences were also assessed (see Appendix).

Table 1 – Research questions and PICOs

What is the optimal staging strategy using MRI?	
P (patient)	Patients presenting with rectal cancer
I (Intervention)	a. MRI for pre-treatment staging b. EUS for pre-treatment staging
R (reference standard)	Histopathology and/or clinical follow-up and/or surgery
T (target disorder)	T-, N- and M-staging
Can local resection or transanal endoscopic microsurgical resection be performed instead of radical resection without compromising the outcome in rectal cancer patients (T1, T2)?	
P (patient)	Patients with T1-T2 rectal cancer
I (Intervention)	a. local resection b. transanal endoscopic microsurgical resection
C (comparison)	Radical resection
O (outcome)	OS, DFS, MFS, LRFS, QoL
When should adjuvant chemotherapy be considered in patients who received neoadjuvant radio(chemo)therapy?	
P (patient)	Patients with stage II, III or IV rectal cancer who received neoadjuvant radio(chemo)therapy
I (intervention)	Adjuvant chemotherapy
C (comparison)	No adjuvant chemotherapy
O (outcome)	OS, DFS, QoL

2.4 Literature search

For each RQ a search for systematic reviews (SR) was conducted in MEDLINE, Embase and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database). If a recent high quality SR was available a search for primary studies published after the search date of the review was performed in MEDLINE, Embase and CENTRAL. If no SR was available, primary studies were searched for in the databases. Members of the GDG were also consulted to identify additional relevant evidence that may have been missed by the search. Detailed search strategies per database can be found in the sections related to the particular RQ in the Appendix. Only articles published in English, German, Dutch and French were included.

2.5 Selection process

Studies were screened on title and abstract using the PICO in- and exclusion criteria and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading the full-text. If no full-text was available, the study was excluded for the final recommendations. Reference lists of the selected studies were hand searched for additional relevant manuscripts. The flow charts illustrating the selection process can also be found in the Appendix.

2.6 Quality appraisal

2.6.1 Systematic reviews

Selected SRs were critically appraised by a single KCE expert using the AMSTAR checklist (see table in Appendix and http://amstar.ca/Amstar_Checklist.php).[24] In doubt, a second KCE expert was consulted.

2.6.2 Primary studies

Critical appraisal of each study was performed by a single KCE expert. In case of doubt, a second KCE expert was consulted. Retrieved diagnostic studies were assessed for the risk of bias with the QUADAS-2 tool.[25] The quality appraisal of randomised controlled trials (RCT) for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias"[26] (see table in Appendix). For each criterion the definitions described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). In the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook.

Study limitations in observational studies were evaluated using GRADE criteria: failure to develop and apply appropriate eligibility criteria (inclusion of control population); under- or overmatching in case-control studies; selection of exposed and unexposed in cohort studies from different populations; flawed measurement of both exposure and outcome; differences in measurement of exposure (e.g., recall bias in case-control studies); differential surveillance for outcome in exposed and unexposed in cohort studies; failure to adequately control confounding; failure of accurate measurement of all known prognostic factors; failure to match for prognostic factors and/or lack of adjustment in statistical analysis, and incomplete follow-up. The tools used for the quality appraisal are reported in the methodology section of the Appendix while the results of the quality appraisal are presented found in the Appendix sections related to each particular RQ.

2.7 Data extraction

For each SR, the search date, publication year, included studies and main results were extracted. For RCTs and longitudinal studies, the following data were extracted: publication year, study population, study intervention, and outcomes. Data extraction was entered in evidence tables using standard KCE templates. Any disagreements were resolved by discussion amongst team members. Evidence tables are reported in the Appendix sections related to the particular RQ.

2.8 Statistical analysis

For each comparison (intervention vs. comparator) separate analyses were performed if data were available. If a recent SR with low risk of bias was available, the results of the review were used and presented in Summary of Findings Tables. If new RCTs were identified, the existing SR and meta-analysis would be updated. This is only feasible if the required data in the review are readily available (i.e. the review reports the 2 by 2 Tables of the included studies). If not feasible, the results of the newly identified RCTs were summarized and presented in Summary of Findings Tables For

diagnostic test accuracy, meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook, (http://srdta.cochrane.org/handbook-dta-reviews) while for treatment, meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook (http://www.cochrane.org/training/cochrane-handbook) using Review Manager Software (Review Manager 2011). Heterogeneity was statistically assessed with χ^2 test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Possible reasons for heterogeneity were explored post-hoc. Sensitivity analysis was performed by removing outliers from the analysis. Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarized qualitatively. Forest plots were reported in each particular section.

2.9 Grading evidence

For each recommendation, we provided its strength and the quality of the supporting evidence.[27] According to GRADE, we classified the quality of evidence into four categories: high, moderate, low, and very low (see tables in Appendix). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

Quality rating for RCTs was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[28]

Observational studies were considered low level of evidence by default (see tables in Appendix). However, the level of evidence of observational studies with no threats to validity could be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient may increase the confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized the Appendix. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles in each particular section when applicable. Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations for diagnosis (RQ1).

2.10 Literature search for patient preferences

Evidence-based practice involves decision-making, based not only on efficacy and effectiveness but also on patient characteristics and preferences. A patient with rectal cancer is faced with difficult and complex decisions that have a crucial impact on health-related quality of life and survival. Studies have shown that medical professionals and patients often place different emphasis on treatment end-points, including side-effects and point out a gap between what both parties regard as most important.[29]

For this topic a systematic search for SRs and meta-analyses on patient preferences for all colorectal cancers was performed, because the topic is relatively new and a search for patient preferences on rectal cancer alone would be too limited. Searches were performed on March 27th, 2015 in the following databases: Medline (through Ovid), Embase and the Cochrane Database of Systematic Reviews. The full search string and the results can be found in the section on patient preferences in the Appendix. These results were used to complete the GRADE assessment for each RQ, if applicable.

2.11 Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by KCE experts and circulated with the evidence tables to the GDG 2 weeks prior to the face-to-face meetings (26th May 2015 and 7th September 2015). Recommendations were changed if important new evidence

supported this change. Based on the discussion during the first meeting a second draft of recommendations was prepared and circulated to the GDG for final approval.

The strength of each recommendation was assigned using the GRADE system (see table Appendix). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences and estimated cost (resource utilization) (see table Appendix). A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention but many would not.[30] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss their values and preferences. Such an in-depth discussion is necessary to empower the patient to make an informed decision.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and therefore its application as quality of care criterion would be inappropriate.[31] For interpretation of “strong” and “weak” recommendations see table in Appendix. No formal cost-effectiveness study was conducted.

2.12 External review

2.12.1 Healthcare professionals

The recommendations prepared by the GDG were circulated to Professional Associations (Table 2). Each association was asked to assign one or two key representatives to act as external reviewers (Stakeholders) of the draft guideline. Eight external experts were involved in the evaluation of the clinical recommendations (20th October 2015). All invited panellists received the scientific reports for the RQs and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of ‘1’ indicating ‘completely disagree’, ‘2’ ‘somewhat disagree’, ‘3’ ‘unsure’, ‘4’ ‘somewhat agree’, and ‘5’ ‘completely agree’ or ‘not applicable’ if they were not familiar with the underlying evidence. If panellists disagreed with the recommendation (score ‘1’ or ‘2’), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts led to rephrasing the clinical recommendations. An overview is provided the scores, comments and how the comments were addressed (see table in Appendix).

Table 2 – List of Professional Associations

- Belgian Society of Medical Oncology - Belgische Vereniging voor Medische Oncologie - Société Belge d'Oncologie Médicale (BSMO)
- Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-OncoloSgie (BVRO - ABRO)
- Belgian Group of Digestive Oncology (BGDO)
- Belgian Society of Surgical Oncology (BSSO)
- Royal Belgian Society of Surgery - Koninklijk Belgisch Genootschap voor Heelkunde (KBGH) - Société Royale Belge de Chirurgie (SRBC)
- Belgian Society of Radiology (BSR)
- Belgische Vereniging voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire
- Belgian Society of Pathology - Belgische Vereniging Anatomopathologie - Société Belge d'Anatomopathologie
- Société Royale Belge de Gastroentérologie
- Société Scientifique de Médecine Générale (SSMG)
- The Belgian Society of Gastrointestinal Endoscopy (BSGIE)
- The Belgian Group for Endoscopic Surgery (BGES)
- Vlaamse Vereniging voor Gastro-enterologie (VVGE)

2.12.2 Patient representatives

Associations of patient representatives (Fondation contre le Cancer/Stichting tegen Kanker and Kom op tegen Kanker) were contacted to invite patient representatives to take part in the scoping and stakeholder meetings (February 10, 2015 and October 20, 2015). A key role for patient representatives is to ensure that patient views and experiences inform the group's work.

2.12.3 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. The scientific content was assessed by three validators on November 9, 2015 (see Colophon).

2.13 Implementation and updating of the guideline

2.13.1 Multidisciplinary approach

In this report we focused on the effectiveness of specific medical interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach by different health care professionals should be encouraged. This approach should not only cover the medical needs of the patient but also their psychosocial needs.

2.13.2 Patient-centered care

The choice of a treatment should not only consider medical aspects but also patient preferences. Patients should always receive timely and comprehensive information about treatment options, advantages and disadvantages.

2.13.3 Barriers and facilitators for implementation

During the stakeholders meeting, the potential barriers and facilitators related to the use of this guideline were discussed. Information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE-report (see KCE website: https://kce.fgov.be/fr).

In this particular case a significant barrier is the termination of the PROCARE program in December 2014. However the College of Oncology will pursue a new PROCARE plan and pursue further registration in the National Cancer Registry. In addition the Belgian Society of Radiology (http://www.bsr-web.be/) will publish the MRI protocol and organize training.

2.13.4 Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to highly codified principles, based on scientific information regularly updated from the international literature. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHDI, professional organizations, hospital managers…) but is not involved in the decision making process itself nor in the execution of the decisions.

The implementation of this guideline will be facilitated/conducted by the College of oncology and the professional associations involved. Dissemination of this guideline is intended by scientific and professional organisations. They can make attractive and user-friendly tools tailored to caregivers groups using diverse channels such as websites or continuing education.

2.13.5 Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that targets all caregivers concerned. It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators. KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organizations and targeted actions to improve the quality if needed.[32] In the present case a protocol for MRI was developed by the GDG.

2.13.6 Guideline update

In view of the rapidly evolving evidence, guidelines should be updated every 5 years. Important new evidence would become available in the meantime, this should be taken into consideration. Potential interest for groups of health practitioners is also considered in this process. This appraisal should lead to a decision on whether to update a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

APPENDIX

APPENDIX 1. SCOPING

Appendix 1.1. Search for guidelines

Table 3 – Websites for guidelines

Institute	Website	Number of hits and reference
GIN guideline resource	http://www.g-i-n.net/	0
IKNL	**www.iknl.nl**	1 [21]
National Guideline Clearinghouse	http://www.guideline.gov/	5 [11, 12, 17, 18, 22]
NCCN	www.nccn.org	1 [10]
NICE guidelines	www.nice.org.uk	1 [20]
SIGN guidelines	www.**sign**.ac.uk	0
Unicancer	http://www.unicancer.fr/	0

Table 4 – Search Strategy for Guidelines

Medline @ Ovid

Date	**2014-12-22**		
Database	**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present**		
Search Strategy	#	***Query***	*Results*
	1	exp Rectal Neoplasms/	**38 981**
	2	(rectal or rectum or colorect*).ab,ti.	**174 342**
	3	(cancer or cancer? or tumour or tumours or tumour or tumours or neoplasm* or carcinom* or adenocarcinom*).ab,ti.	**2 218 396**

	4	((rectal or rectum or colorect*) adj3 (cancer or cancer? or tumour or tumours or tumour or tumours or neoplasm* or carcinom* or adenocarcinom*)).ab,ti.	**100 218**
	5	1 or 4	**116 431**
	6	practice guideline/	**20 171**
	7	(practice or clinical).ab,ti.	**27 59 790**
	8	guideline?.ab,ti.	**206 999**
	9	((practice or clinical) adj3 guideline?).ab,ti.	**29 301**
	10	exp Practice Guidelines as Topic/	**85 192**
	11	6 or 9 or 10	**119 980**
	12	5 and 11	**1 425**
	13	limit 12 to yr="2007 -Current"	**871**
	14	**limit 13 to systematic reviews**	**213**

Embase @ Embase.com

Date	**2014-12-22**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	**#**	***Query***	*Results*
	#1	'rectum tumour'/exp	**161 251**
	#2	rectal:ab,ti OR rectum:ab,ti OR colorect*:ab,ti	**228 526**
	#3	cancer:ab,ti OR cancers:ab,ti OR tumour:ab,ti OR tumours:ab,ti OR tumour:ab,ti OR tumours:ab,ti OR neoplasm*:ab,ti OR carcinom*:ab,ti OR adenocarcinom*:ab,ti	**2 697 935**

#4	((rectal OR rectum OR colorect*) NEAR/3 (cancer OR cancer? OR tumour OR tumours OR tumour OR tumours OR neoplasm* OR carcinom* OR adenocarcinom*)):ab,ti	**131 307**
#5	#1 OR #4	**178,293**
#6	'practice guideline'/exp	**319,541**
#7	practice:ab,ti OR clinical:ab,ti	**3 520 175**
#8	guideline:ab,ti OR guidelines:ab,ti	**289 379**
#9	((practice OR clinical) NEAR/3 (guideline OR guidelines)):ab,ti	**38 053**
#10	#6 OR #9	**333 005**
#11	#5 AND #10	**4 500**
#12	#5 AND #10 AND [2007-2015]/py	**2 717**
#13	'good clinical practice'/exp	**7 381**
#14	#9 OR #13	**44 907**
#15	#5 AND #14	**678**
#16	#5 AND #14 AND [2007-2015]/py	**468**
#17	[medline]/lim	**21 506 860**
#18	#16 NOT #17	**205**
#19	[cochrane review]/lim OR 'systematic review' OR 'meta analyse' OR [meta analysis]/lim OR [systematic review]/lim OR 'meta analyses' OR 'meta analysis' OR 'guideline' OR 'guidelines'	**606 021**
#20	**#18 AND #19**	**196**

Cochrane Database of Systematic Reviews

Date	**2014-12-22**		
Database	**Cochrane**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	MeSH descriptor: [Rectal Neoplasms] explode all trees	**1 218**
	#2	(rectal or rectum or colorect*):ab,ti	**11 916**
	#3	(cancer or cancers or tumour or tumours or tumour or tumours or neoplasm* or carcinom* or adenocarcinom*):ab,ti	**76 912**
	#4	((rectal or rectum or colorect*) near/3 (cancer or cancers or tumour or tumours or tumour or tumours or neoplasm* or carcinom* or adenocarcinom*)):ab,ti	**6 601**
	#5	#1 or #4	**6 857**
	#6	MeSH descriptor: [Practice Guideline] explode all trees	**15**
	#7	MeSH descriptor: [Practice Guidelines as Topic] explode all trees	**1 759**
	#8	((practice or clinical) near/3 (guideline or guidelines)):ab,ti	**1 836**
	#9	#6 or #7 or #8	**3 226**
	#10	#5 and #9 Publication Year from 2007 to 2014	**17**
	#11	**#5 and #9**	**32**

Appendix 1.2. Selection and critical appraisal

A rapid assessment was used, selecting guidelines that scored positively on question 7, 8 and 10 of the AGREE II evaluation tool.

Table 5 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II
Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of Development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Critical appraisal of clinical practice guidelines - AGREE II
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Appendix 1.3. Scoping by GDG

Table 6 – Scoring of research questions by GDG

RQ (based on Procare 2007)	NICE 2011	IKNL 2014	other GL	TOTAL SCORE	COMMENTS
1. Diagnosis and staging			Monson,Pox,Vogl	0	
a. What method should be used for the detection of synchronous colonic lesions (polyps, cancer) in patients with rectal cancer?				4	
b. Are tumour markers useful staging tools in patients with rectal cancer?				1	
c. What imaging technique(s) can be recommended for the detection of metastatic disease in patients with rectal cancer?		X	Beets-Tan	0	
d. What imaging technique(s) can be recommended for the locoregional cTN staging of patients with rectal cancer?		X	Beets-Tan	7	representing the Belgian Society of Gastrointestinal Endoscopy, questions about endoscopy and rectal cancer are my priorities
2. Neoadjuvant treatment		x primary RC therapy	Konski (ACR recurrent RC) Monson,Pox	0	
a. Can preoperative radiotherapy improve the outcome in patients with resectable rectal cancer compared to surgery alone?	X			4	a more selective use of (chemo)radiotherapy should be discussed
b. Is preoperative chemoradiotherapy better than preoperative radiotherapy alone in the outcome of patients with resectable rectal cancer?	X			0	

c. Is preoperative (chemo)radiotherapy better than postoperative chemoradiotherapy in the outcome of patients with resectable rectal cancer?	X	0	
d. Is 5-FU continuous infusion superior to bolus 5-FU in combination with preoperative radiotherapy in the outcome of patients with resectable rectal cancer?		0	
e. Is intravenous 5-FU better than oral 5-FU in the outcome of patients with resectable rectal cancer?		0	
f. Is a long course of preoperative (chemo)radiation better than a short course of preoperative radiation in the outcome of patients with resectable rectal cancer?	X	3	
g. Is a long treatment interval between preoperative (chemo)radiation and surgery better than a short interval in the outcome of patients with resectable rectal cancer?	X	17	While an interval of 8 to 12 weeks after a long course chemoradition is commonly accepted, it is suggested than an even longer interval could improve on the downstaging. Likewise, while it is stated that surgery should follow directly after a short course radiation, some surgical teams are now observing a long interval before the surgery. New evidence is available and in favour of a longer interval the approach in case of clinical 'complete' response after (chemo)radiation or chemotherapy with long interval to planned surgery should be discussed or inserted as a new GL
h. Is there any benefit from alternative regimens of preoperative (chemo)radiotherapy compared to the standard regimen of (chemo)radiotherapy (short course or long course) in the outcome ofpatients with resectable rectal cancer? What is the role of brachytherapy/contact X-ray therapy in the preoperative treatment of resectable rectal cancer?		15	Even though Oxaliplatin is not recognised as being part of the standard regimen in preoperative long course chemoradiation, it is not uncommon to see patient, especially young ones, being treated with a combination such as Folfox. since our guidelines, several Phase III studies have been performed and hould be added, also brachy is used more often.
i. Is restaging after preoperative treatment useful in patients with resectable rectal cancer?		6	Can we change an APR surgery for an Anterior Resection if there is a downsizing after chemoradiation and that the distal margin of the tumour to the anal sphincter goes from nul to 1cm. And therefore shall we need to restage

				after chemoradiation. what are the consequences: will it change therapy? Which examinations?
j. What is the role of (chemo)radiotherapy in patients with unresectable rectal cancer?	X		6	
3. Surgery		Russo, Jones (ACR criteria) Monson,Pox	0	
a. Can urinary or sexual dysfunction be avoided by good quality total mesorectal excision (TME) sphincter saving or abdominoperineal resection in rectal cancer patients for whom curative surgery is scheduled?			0	
b. Can postoperative morbidity be reduced by preoperative bowel preparation in rectal cancer patients for whom curative surgery is scheduled?			1	Based on meta-analysis we lost the habit of bowel preparation for colon surgery. What about rectal surgery?
c. Can postoperative deep venous thrombosis (DVT) be reduced by perioperative thromboprophylaxis in rectal cancer patients for whom curative surgery is scheduled?			0	
d. Can postoperative septic complications be reduced by antibiotic prophylaxis in rectal cancer patients for whom curative surgery is scheduled?			0	
e. Can preoperative stoma counselling, including stoma sitting, improve postoperative quality of life in rectal cancer patients for whom curative surgery is scheduled?	X		4	Objectieve en volledige informatie verstrekking is een vereiste zodat de patient mee kan beslissen over zijn eigen behandeling. should be 'stoma siting'
f. What is the impact of high versus low ligation of the inferior mesenteric artery on outcome in rectal cancer patients for whom curative surgery is scheduled?			1	
g. What is the impact of lateral lymphatic dissection (iliac nodes) on outcome in rectal cancer patients for whom curative surgery is scheduled?			1	new data available (but message/GL unchanged)
h. Can sphincter saving operation be performed for rectal cancer of the lower third of the rectum without compromising the (oncological and functional) outcome in patients for whom curative surgery is scheduled?			0	

i. Can laparoscopic resection be performed without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?	X	2	should also discuss robot-assisted lap surgery
j. Does inadvertent perforation of the rectum during surgery influence oncological outcome in rectal cancer patients for whom curative surgery is scheduled?		0	
k. Does rectal stump wash-out prior to anastomosis decrease local recurrence in rectal cancer patients for whom curative surgery is scheduled?		0	
l. Should a colonic pouch, a coloplasty or a straight coloanal anastomosis be performed for optimal functional outcome in rectal cancer patients for whom curative surgery is scheduled?		0	
m. Should a temporary defunctioning stoma routinely or selectively be constructed at restorative proctectomy in order to reduce clinical leak rate in rectal cancer patients for whom curative surgery is scheduled?		6	guidelines for the surgeon! new data avilable (but approx same message/GL)
n. Can a local resection or transanal endoscopic microsurgical resection be performed instead of a radical resection without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?		19	Different radiochemotherapy + local excision treatment strategies are currently being developed. Less invasive and less radical surgical treatment has become an important issue as it potentially offers cure without causing significant and irreversible faecal, urinary and sexual impairment. organ preservation is introduced in the clinic without a lot of scientific evidence
o. Is stenting an appropriate alternative for stoma construction as a bridge to radical surgery in case of stenosing rectal cancer?		5	oncological safety?
p. Is stenting a valid alternative for stoma construction in a palliative setting?		4	
4. Pathology	X		
a. How should a rectal cancer resection specimen be assessed macroscopically (with specific criteria for the evaluation of TME quality)?		4	

b. How should a rectal cancer resection specimen be assessed microscopically?				3	
c. What are the data to be reported by the pathologist?				5	
5. Adjuvant treatment		X	Monson,Pox		
a. In patients who received neoadjuvant radio(chemo)therapy, when should adjuvant chemotherapy be considered?	X			25	Question that still remains with poor evidence answer remains unclear, meta-analysis is performed since our guidelines after meta-analysis Lancet oncology, published online 12/01/2015 new data available
b. In patients who received neoadjuvant radio(chemo)therapy, what chemotherapy is to be recommended?	X			5	could be integrated with 5a; new data available
c. In patients who did not receive neoadjuvant radio(chemo)therapy, when should adjuvant treatment be considered?	X			3	
d. In patients who did not receive neoadjuvant radio(chemo)therapy, what type of adjuvant treatment and regimen is to be recommended: radiotherapy, chemotherapy or combined radiochemotherapy?	X			1	might need an update after Mercury
6. Follow-up		X	Pox		
a. Has follow-up an impact on survival and quality of life in patients curatively treated for rectal cancer?	X			3	Patiënten met rectum kanker dienen goed medisch en psychosociaal omringd te worden zodat een zo hoog mogelijke levenskwaliteit gegarandeerd kan worden.
b. What clinical, biochemical or technical investigations have to be done in terms of local recurrence, distant recurrence and resectability of recurrence in patients curatively treated for rectal cancer?	X			2	
c. How frequently and for how long clinical, biochemical or technical investigations have to be done in terms of local recurrence, distant recurrence in patients curatively treated for rectal cancer?	X			4	
7. Metastatic disease			Goodman		

a. What diagnostic tools can be used to determine the resectability of a metastatic disease? What are the resectability criteria?	X		
b. What is the best management in patients with resectable primary tumour and resectable metastases?	X	16	New evidence available. new data on surgery first vs chemo first
c. Is radical treatment of a resectable primary tumour useful in patients with non resectable metastases?		0	Is resection of the rectum the best palliative treatment in rectal cancer for preventing the installation of the rectal syndrome?
d. Does first-line chemotherapy alone as compared to observation have an impact on prognosis in patients with synchronous or metachronous non resectable metastases?	X	0	new data on new drug combinations are available
e. Does second-line chemotherapy alone as compared to observation have an impact on prognosis in patients with synchronous or metachronous non resectable metastases?	X	0	
f. What combination(s) should be considered for first- and second line chemotherapy?	X	**0**	new data avilable
g. How to manage non-resectable metastatic rectal cancer?	X	**0**	new data on new drug combinations are available
h. What is the management of isolated peritoneal carcinomatosis?		**4**	
8. Additional RQ proposed by GDG			
Patient values and preferences: what is the optimum psychosocial care for a patient with rectal cancer, during and after the disease trajectory?			Evenwichtige en begrijpelijke informatie over de pro's en contra's van de verschillende behandelingsmogelijkheden: operatie, bestraling, chemotherapie, stoma. de mogelijke bijwerkingen van behandeling zoals bv incontintentie, diarree, constipatie, opgeblazen gevoel, winderigheid, voedingsvoorschriften, verzorging van stoma,.... Correcte en begrijpelijke informatieverstrekking aan patiënten met rectum kanker. Ondersteuning bij het nemen van beslissingen. -Er is nood aan goede psychosociale begeleiding (professionelen en lotgenotencontact) niet enkel in het ziekenhuis maar ook als de patient weer in de thuissituatie is.

Wait and see in case of complete clinical response - define complete clinical resp - mandatory resection of primary tumour - ethical aspects of surveillance - prospective registry			
Definition of Risk for local recurrence and for metastasis			
What is the optimal concomitant chemotherapeutic in case of neoadjuvant radiotherapy			could replace 2d and 2e (that could be integrated into a single GL)
Is neoadjuvant chemotherapy as performant as chemoradiation for resectable and non-resectable tumours?			
what approach in case of clinical 'complete' response after (chemo)radiation or chemotherapy with long interval to planned surgery? cfr 2g and 2h	a lot of recent literature about a 'wait and see' approach in case of cCR		
Application of a standardized pathology report			
Which TNM-classification should be applied (5th or 7th edition)?			
Should molecular analysis routinely be performed and which tests should be done?			
the indications of local excision and the choice between surgical or endoscopic techniques (knowing the development of TEM and piecemeal EMR and ESD: endoscopic submucosal dissection)			
5 a & b could be 1 RQ and 7 b & c could be 1 RQ			

APPENDIX 2. CRITICAL APPRAISAL CHECKLISTS FOR SYSTEMATIC REVIEWS AND PRIMARY STUDIES

Appendix 2.1. Systematic reviews

AMSTAR criteria were used to assess systematic reviews.

Table 7 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Appendix 2.2. Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS Tool.

Table 8 – The QUADAS tool

Item	Label	Yes	No	Unclear	Not applicable
1.	Was the spectrum of patients representatives of the patients who will receive the test in practice?				
2.	Were selection criteria clearly described?				
3.	Is the reference standard likely to correctly classify the target condition?				
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?				
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?				
6.	Did patients receive the same reference standard regardless of the index test result?				
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?				
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?				
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?				
10.	Were the index test results interpreted without knowledge of the results of the reference standard?				
11.	Were the reference standard results interpreted without knowledge of the results of the index test?				
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?				
13.	Were uninterpretable/ intermediate test results reported?				
14.	Were withdrawals from the study explained?				

Appendix 2.3. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool.

Table 9 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

To conduct the quality appraisal of comparative cohort studies, the following tool was used.

Table 10 – Quality appraisal of selected primary studies (cohort studies)

Domains	Options	Ref 1	Ref 2	Ref 3	Ref 4	Ref 5
Domain 1: Selection bias						
• Can selection bias sufficiently be excluded?	Yes/No/Insufficient info to assess					
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes/No/Insufficient info to assess					
Domain 2: Detection bias						
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes/No/Insufficient info to assess					
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes/No/Insufficient info to assess					
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	Yes/No/Insufficient info to assess					
• Is the assessment of outcome made blind to exposure status?	Yes/No/Insufficient info to assess					
If no to question 6, does this have an impact on the assessment of the outcome?	Yes/No/ Not possible in this type of exposure /Insufficient info to assess					
• Is the follow-up sufficiently long to measure all relevant outcomes?	Yes/No/Insufficient info to assess					
Domain 3: Attrition bias						
• Can selective loss-to-follow-up be sufficiently excluded?	Yes/No/Insufficient info to assess					

APPENDIX 3. GRADING EVIDENCE

Table 11 – A summary of the GRADE approach to grading the quality of evidence for each outcome.

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⨁⨁⨁⨁) Moderate (⨁⨁⨁⊖) Low (⨁⨁⊖⊖) Very low (⨁⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 12 – Levels of evidence according to the GRADE system.

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
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	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 13 – Downgrading the quality rating of evidence using GRADE.

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

APPENDIX 4. PATIENT PREFERENCES

Appendix 4.1. Introduction

Evidence-based practice involves decision-making, based not only on efficacy and effectiveness, but also on patient characteristics and preferences. For a rectal cancer patients the decisions needed to take during a treatment pathway are often complex, and can have a crucial impact on health-related quality of life and on survival. Studies have shown that the medical professional and the patients often place different emphasis on the end-points of a treatment, including side-effects, and that there continuous to be a gap between what the patient considers more important and what is regarded as most important amongst the medical professionals.[29]

Appendix 4.2. Methods

For this topic a systematic search for SRs and meta-analysis on patient preferences for all colorectal cancers were performed, because it was assumed that the topic is relatively new, and that it therefore would be too limited to search for patient preferences on rectum cancer alone, as well as it would be too limited to perform a search for patient preferences per stand-alone research question. Searches were performed on February 27th, 2014 in the following databases: Medline (through Ovid), Embase and the Cochrane Database of Systematic Reviews. The full search string for this supplementary research question can be found in the Appendices. This search on patient preferences resulted in 211 hits. After screening of titles and abstracts 2 SRs were retrieved for a full-text review. Both were aligned with the research questions and were included.

Appendix 4.3. Evidence description

The most recent SR, published by Currie in August 2014[33] with a search up to March, 2014, aimed to assess patient preference elicitation methods in the treatment of colorectal cancer. The authors reviewed articles using a validated instrument to define patient preferences for any aspect of colorectal cancer treatment. Eight empirical studies were included, and evidence was synthesized in two domains:

- Surgical management preferences
- Adjuvant treatment preferences

The second systematic review, published by Damm in April, 2014[34] with a search up to September 2012, performed a broader search with an aim to identify all studies where preferences had been stated by colorectal cancer patients concerning treatment or the decision-making involvement process. This review identified a total of 19 publications, six of these were the same as in the recent review, however, two studies by Blinman (2012) and Hofmann (2010) identified by the Currie review were not included by Damm, probably because these studies were published after the end of this review's search date. Similar to the review by Currie, the review by Damm synthesized the evidence in two domains being:

- Treatment preferences
- Preferences for treatment decision-making involvement

For readability and relevance in presentation of the evidence, the structure from both review are kept and information merged into three sections, namely a section on surgical management preferences, a section on adjuvant treatment preferences and, finally, a section on preferences for treatment decision-making involvement. Studies that do not fall into these categories are only described briefly in the text or not described.

Appendix 4.4. Surgical management preferences

Surgical management preferences were assessed in five studies and results are presented in Table 14.

Table 14 – Patient preferences regarding surgical management.

Study	Bossema et al. (info retrieved from Currie, 2014, [33])	Matsuoka et al. (info retrieved from Damm, 2014, [34])	Zolziak et al. (info retrieved from Currie, 2014, [33])	Harrison et al. (info retrieved from Currie, 2014, [33])	Solomon et al. (info retrieved from Currie, 2014, [33])
Clinical situation/choice	Mid/low rectal cancer, LAR or APR	Rectal cancer	Mid/low rectal cancer, LAR or APR	Mid/low rectal cancer, LAR or APR	Low T1/T2 rectal cancer, local excision or APR
Preference instrument used	Time trade-off	Treatment outcome choice	Treatment choice method	Time trade-off	Time trade-off/standard gamble
Number of patients studies (n)	122	45	249	103	100
Info presented to the patient	LAR risk higher levels of incontinence but no permanent stoma. APR carries no risk of incontinence (but stoma)	Patients were asked whether they preferred stoma or an evacuatory disorder following surgery	APR results in permanent stoma but LAR may have higher complications and lead to incontinence and bowel dysfunction	APR results in permanent stoma but LAR may compromise long-term survival	Local excision may lead to reduced survival but will avoid permanent stoma
Patient preference	Patients most likely to select LAR	Even when patients had evacuatory disorder they preferred to live without stoma	Patients most likely to select LAR	Patients prepared to trade reduced survival to avoid stoma	Most patient prepared to gamble reduced survival to avoid stoma
Predictors of preference	Previous APR meant stoma was viewed less negatively	-	Previous APR meant stoma was viewed less negatively	Knowing someone with stoma meant APR was viewed even more negatively	Not assessed
Non-predictors	-	-	Age, gender, education level, employment	Education level	-

APR= abdominoperineal excision of the rectum, LAR= low anterior resection
As displayed the evidence suggest that patients are prepared to trade significant reduction in life expectancy to avoid complications after surgery, in particular stoma.

Appendix 4.5. Adjuvant treatment preferences

Adjuvant treatment preferences were assessed in seven studies, and results are presented in Table 15.

Table 15 – Patient preferences regarding adjuvant treatment.

Study	Blinman et al. (info retrieved from Currie, 2014,[33])	Hofmann et al. (info retrieved from Currie, 2014,[33])	Couture et al. (info retrieved from Currie, 2014, [33])	Harrison et al. (info retrieved from Currie, 2014, [33])	Borner et al. (info retrieved from Damm, 2014, [34])	Pfeiffer et al. (info retrieved from Damm, 2014, [34])	Twelves et al. (info retrieved from Damm, 2014, [34])
Clinical situation	Adjuvant chemotherapy for Stage II-III colon cancer	Adjuvant chemotherapy for Stage III colon cancer	Adjuvant radiotherapy following rectal cancer resection	Adjuvant radiotherapy following Stage II-III rectal cancer resection	Advanced colorectal cancer	Colorectal cancer patients	Advanced colorectal cancer
Preference instrument used	Standard gamble	Decision board/treatment choice method	Time trade-off	Time trade-off	One choice (op/i.v.) after both experiences (preference for oral UFT/leucovorin(LV) vs. intravenous 5-FU/LV chemotherapy)	One choice after both experiences (oral capecitabine or i.v. 5-Nordic FL/LV)	One choice, before and after treatment preferences (oral capecitabine or i.v. 5-Nordic FL/LV)
Number of patients studies (n)	123	102	47	103	37	49	97
Info presented to the patient	Adjuvant chemotherapy may extend survival (varied from small to large increase) but may impair QOL through side-effects	Adjuvant chemotherapy may increase changes of survival (% benefit varied), but would risk treatment side-effects	Adjuvant radiotherapy would reduce local recurrence, but would not affect survival and may have effects on bowel function	Adjuvant radiotherapy would reduce local recurrence, but would not affect survival and may have effects on bowel function	-	-	-

Patient preference	Even small increases in survival were worth side effect risk	Most patients judged small survival benefits were worth side-effect risk	Adjuvant therapy had to reduce local recurrence by large percentage to justify impact on QoL	Patients would trade considerable life expectancy to avoid adjuvant therapy that affected quality of life but had no survival impact	84% preferred oral over i.v. Reasons: taking medication at home, less stomatitis and diarrhoea, pill over injection	61% preferred the Nordic FL regimen and 39% capecitabine	Before treatment: 95% preferred oral treatment; after treatment: 64%. Reasons: convenience, home-based administration and tablet formulation
Predictors of preference	Tertiary education and older age required larger survival benefits	Not assessed	Previous radiotherapy patients viewed radiotherapy less negatively	Tertiary education prepared to trade larger survival impact to avoid radiotherapy	Not assessed	Not assessed	Not assessed
Non-predictors	Gender, employment, family	Not assessed	Age, gender	Age, gender, employment	Not assessed	Not assessed	Not assessed

As displayed the evidence suggests that, in the adjuvant setting, patients are prepared to risk significant treatment side-effects to gain small potential increases in life-expectancy and change of survival. However, where adjuvant (or neo-adjuvant) therapy comes with a risk of decrease in function, patients generally prefer to forgo potential increases in survival to improve bowel function (and through that QoL). Two studies find that patients prefer to take oral medication (chemotherapy) in comparison with receiving this in an intravenous form. However, one study concludes the opposite.

Appendix 4.6. Decision-making involvement

Decision-making involvement was only described in the review by Damm et al.[34] Decision-making involvement assessed in in six studies and results are presented in Table 16.

Table 16 – Patient preferences regarding decision making involvement

Study	Beaver et al.	Elkin et al.	Pieterse et al.	Ramfelt et al.	Salkeld et al.	Sanders et al.
Clinical situation	Colorectal cancer	Metastatic colorectal cancer	Rectal cancer	Colorectal and rectal cancer	Colorectal cancer	Bowel cancer
Method used	Semi-structured interviews	Control preferences scale	Control preferences scale	Control preferences scale	Control preferences scale	Semi-structured interviews
Number of patients studies (n)	41	73	70	55	175	37
Study aim	Patient views on participation in treatment, physical and psychological care decisions	Preferences for involvement in treatment decision making among elderly patients	Assess the preferred role of oncologists and cancer patients in deciding about treatment	Compare preferences about the degree of participation in treatment decision-making before and after surgery	Importance of decision- making aspects	Patient's experience of bowel cancer and the treatment decision-making process
Patient preference	Participation in decision-making was about being informed and feeling involved in the consultation process	52% favoured a passive, 23% a shared role and 25% an active role	Clinicians preferred the shared role (73%), patients' role preferences were more equally spread out	Before surgery: 24% favoured a passive, 71% a shared role and 0% an active role. After surgery: 22% favoured a passive, 75% a shared role and 2% an active role	55% favoured a passive, 29% a shared role and 14% an active role	Most patients preferred a limited role in the treatment decision-making
Relevant subgroup results	-	-	Significant association between a lower education in patients and a preference to relinquish decisional control	-	Women were more likely to prefer shared decision-making. Older patients and those who had undergone adjuvant radiotherapy were more likely to prefer a passive role	

The Currie review concludes that regarding adjuvant therapy “most patients judge a moderate survival benefit to be sufficient to make adjuvant therapy worthwhile”. On the contrary the review concludes that patients “are willing to trade a potential reduction in life expectancy and survival to avoid unwanted surgical sequelae”.[33]The Damm review concludes that “although colorectal cancer patients do have preferences regarding different treatment options and outcomes, these are not homogeneous and seem to also depend on personal factors, including age and gender”. Additionally, the review concludes that “despite the existence of preferences the majority of patients prefer to take a passive role in the decision-making process, which in part may be explained by the severity of the disease”.[34] These data were taken into account when formulating recommendations for the three RQs.

APPENDIX 5. FORMULATION OF RECOMMENDATIONS

Appendix 5.1. Evaluation of the recommendations

Table 17 – Strength of recommendation according to the GRADE system.

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Table 18 – Factors that influence the strength of a recommendation.

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605–14.
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Table 19 – Interpretation of strong and conditional (weak)* recommendations.

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms "conditional" and "weak" can be used synonymously*
Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Appendix 5.2. Meeting with stakeholders and patient representatives

Table 20 – Recommendations scored by stakeholders

STAGING WITH MRI OR EUS	Offer MRI to assess the risk of local recurrence, as determined by anticipated circumferential resection margin, tumour and lymph node staging and extramural venous invasion (EMVI), to all patients with rectal cancer unless it is contraindicated.	4	5	NA	5	5	5	4	5	4,8	5	100%	
	Offer endorectal ultrasound to patients with rectal cancer if MRI shows disease amenable to local excision or if MRI is contraindicated.	3	5	NA	5	4	5	3	5	4,4	5	80%	SH5: because of rather low accuracy of MRI and EUS, combination of the two examinations can be considered. Also if doubt about sfincter invasion.
LOCAL EXCISION COMPARED TO RADICAL EXCISION FOR LOCALIZED RECTUM CANCER	There is insufficient evidence to recommend local resection or radical resection for localised rectum cancer.	3	5	NA	5	1	1	1	5	3	3	40%	SH5: local resection only for Tis en T1sm1
	Local resection should not be used in patients with T2 rectal cancer.	5	5	NA	5	5	5	5	5	5	5	100%	
	TEMS can be used for T1A by an experienced specialist and on the condition of an adequate surveillance.	5	3	NA	5	4	5	3	5	4,4	5	80%	SH2: What does it means "experienced specialist"? SH5: T1A is not mentioned in TNM, 7th edition. More used is sm1, sm2, sm3.Local resection (TEMS or ESD,) for sm1
	T1B rectal cancers (staged on pathology report) should be discussed by a multidisciplinary team	5	5	NA	5	4	5	4	5	4,8	5	100%	SH5: T1B not mentioned in TNM, 7th edition. More used is sm1(3 % pos N, sm2(8 % pos N), sm3(23 %
ADJUVANT CHEMOTHERAPY (CT) AFTER NEOADJUVANT TREATMENT	Based on the current available evidence, no recommendation can be made in favour or against the use of adjuvant CT in patients with rectum cancer who received CRT.	5	4	NA	5	4	NA	4	5	4,5	4,5	100%	SH5: if adjuvant chemotherapy considered, probably best therapy is Folfox and not 5-FU.
		1											completely disagree
		2											somewhat disagree
		3											unsure
		4											somewhat agree
		5											completely agree
		NA											not applicable to me

Table 21 – Recommendations rephrased by stakeholders

Recommendation(s)
Offer MRI to assess the risk of local recurrence, as determined by anticipated circumferential resection margin, tumour and lymph node staging and extramural venous invasion (EMVI), to all patients with rectal cancer unless it is contraindicated.
Offer endorectal ultrasound to patients with rectal cancer if MRI shows disease amenable to local excision, additional clinical information is needed, or if MRI is contraindicated.
Radical resection should be used in patients with T2 rectal cancer.
'En bloc' complete local resection is considered sufficient when pathology report and staging confirms pT1 sm1 - Discussion by a multidisciplinary team and adequate surveillance is mandatory -
pT1 sm2 sm 3 should be discussed by a multidisciplinary team, if no contraindication radical surgery is recommended.
Based on the current available evidence, no recommendation can be made in favour or against the use of adjuvant chemotherapy in patients with rectal cancer who received CRT.

APPENDIX 6. TNM CLASSIFICATION

Appendix 6.1. TNM Clinical classification

Table 22 – TNM Classification of Tumours - IUAC 7th edition: RECTUM (C20)

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa or into non-peritonealized perirectal tissues
T4	Tumour directly invades other organs or structures (T4a) and/or perforates visceral peritoneum (T4b)
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	N1 Metastasis in 1-3 regional lymph nodes
N2	N2 Metastasis in 4 or more regional lymph nodes
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis M1a one organ M1b more than one organ or the peritoneum

Appendix 6.2. pTNM Pathological Classification

Table 23 – pTNM Classification of Tumours - IUAC 7th edition

pT – Primary Tumour
pT is the pathological classification corresponding to the T categories
pN – Regional lymph nodes
pN is the pathological classification corresponding to the N categories
pM- Distant metastases
pM1 Distant metastasis microscopically confirmed

Appendix 6.3. Stage grouping Rectum Cancer - IUAC 7th edition

Stage 0	Tis	N0	M0
Stage I	T1,T2*	N0	M0
Stage II	T3,T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1	M0
Stage IIIA	T1,T2	N1, N2	M0
	T1	N2a	M0
Stage IIIB	T3,T4a	N1	M0
	T2,T3	N2a	M0
	T1,T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3,T4a	N2b	M0
	T4b	N1,N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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