A report on treatment options in advanced rectal carcinoma: neoadjuvant treatment or primary resection for Universitätsklinikum Schleswig-Holstein/Campus Kiel

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LIST OF ABBREVIATIONS

APR	Abdominoperineal resection
AR	Anterior resection
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CPG	Clinical practice guideline
CRD	Centre for Reviews and Dissemination
DFS	Disease-free survival
DARE	Database of Abstracts of Reviews of Effects
FAQ	Frequently asked question
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray
HR	Hazard ratio
HTA	Health technology assessment
ISR	Intersphincteric resection
KSR	Kleijnen Systematic Reviews
LAR	Low anterior resection
MA	Meta-analysis
N/A	Not applicable
NEO-RC	Neoadjuvant radiochemotherapy
NEO-RT	Neoadjuvant radiotherapy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
OS	Overall survival
pCR	Pathological complete response
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Transparent Reporting of Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
SA	Surgery alone
SDM	Shared decision making
SR	Systematic review
SUR	Surgery
TME	Total mesorectal excision
TNT	Total neoadjuvant therapy
UICC	Union Internationale Contre le Cancer
UKSH	Universitätsklinikum Schleswig-Holstein

1. PROJECT OBJECTIVES

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews Ltd (KSR) has prepared this evidence report with a synthesis of the relevant evidence of treatment options for advanced rectal carcinoma: neoadjuvant treatment or primary resection.

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with surgeons at Universitätsklinikum Schleswig-Holstein (UKSH)/Campus Kiel. These questions pertain to the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Systematic reviews (SRs), clinical practice guidelines (CPGs) and primary research evaluated herein aim to inform patients, clinicians, researchers, and health policy makers on relevant evidence pertaining to neoadjuvant treatment or primary resection for patients with advanced rectal carcinoma.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Adult patients with rectal carcinoma of the lowest/medium third (up to 12 cm from anocutaneous line) in UICC stage II/III	N/A
Intervention/ comparator	1. Neoadjuvant radiochemotherapy (5 ½ weeks) followed by surgery (mostly 8-12 weeks later) 2. Neoadjuvant short-term radiotherapy (1 week: 5x 5 Gy) followed by surgery, either within 10 days from radiation initiation or about 4-8 weeks later 3. Surgery without neoadjuvant treatment i.e., primary resection	N/A
Outcomes	• Overall survival • Disease free survival • Local tumour recurrence • Pathological complete response • Metastases • Mortality • Both long and short-term risks of the interventions • Sphincter preservation • Quality of life	N/A
Study design	Systematic reviews, clinical practice guidelines, primary research	Narrative reviews; expert opinions; letters' overviews of reviews
Gy = Gray; N/A = not applicable; UICC = Union Internationale Contre le Cancer		

2.2 FREQUENTLY ASKED QUESTIONS

The following frequently asked questions (FAQs) were identified:

1. What does the treatment involve?
2. When is the treatment especially suitable for me?
3. Does the treatment (neoadjuvant radiotherapy or neoadjuvant radiochemotherapy) influence the type of surgery chosen? Sphincter-preserving or not?
4. How will treatment influence my rectal tumour? Will I respond to treatment? Is there a chance for complete remission?
5. Will treatment reduce my risk for tumour recurrence?
6. Will the treatment prolong my life?
7. Are there long-term negative effects of treatment to be expected?
8. How will treatment impact my quality of life?

2.3 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews and evidence-based guidelines regarding surgery for rectal carcinoma with and without neoadjuvant treatment. To inform FAQs a second targeted database search on rectal carcinoma plus surgery/neoadjuvant and shared decision making was also undertaken.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2015-2021. The targeted searches on shared decision-making were also limited to 2016-2021 as current and up-to-date evidence in this area was most relevant. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

2.4.1 Systematic reviews and guidelines

The following systematic review specific databases were searched from 2015 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2021/01/Iss1
- Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk): up to 2015/03
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): up to 2018/03
- INAHTA (https://database.inahta.org/): up to 2021/01/28
- KSR Evidence (KSR): up to 2021/01/27
- Epistemonikos (www.epistemonikos.org): up to 2021/01/27

The following guidelines resources were searched from 2015 to present:

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 2021/01/26
- NHS Evidence (www.evidence.nhs.uk): up to 2021/01/27
- ECRI Guidelines Trust (https://guidelines.ecri.org/): up to 2021/01/28

- NICE (www.nice.org.uk): up to 2021/01/26
- TRIP Database (https://www.tripdatabase.com/): up to 2021/01/26

Full details of all search strategies are presented in Appendix 1.

2.4.2 Targeted searches

To identify questions relevant to shared decision making, targeted searches were undertaken in the following databases from 2016 to present:

- EMBASE (Ovid): 1974-2021/01/27
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2021/01/27

Full details of all search strategies are presented in Appendix 1.

2.4.3 Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.4.4 Supplementary searches

Reference lists of all included studies were checked for relevant studies. In addition, internet searches were performed to add qualitative patient-related information to inform the more narrative FAQs.

2.5 STUDY SELECTION AND DATA EXTRACTION

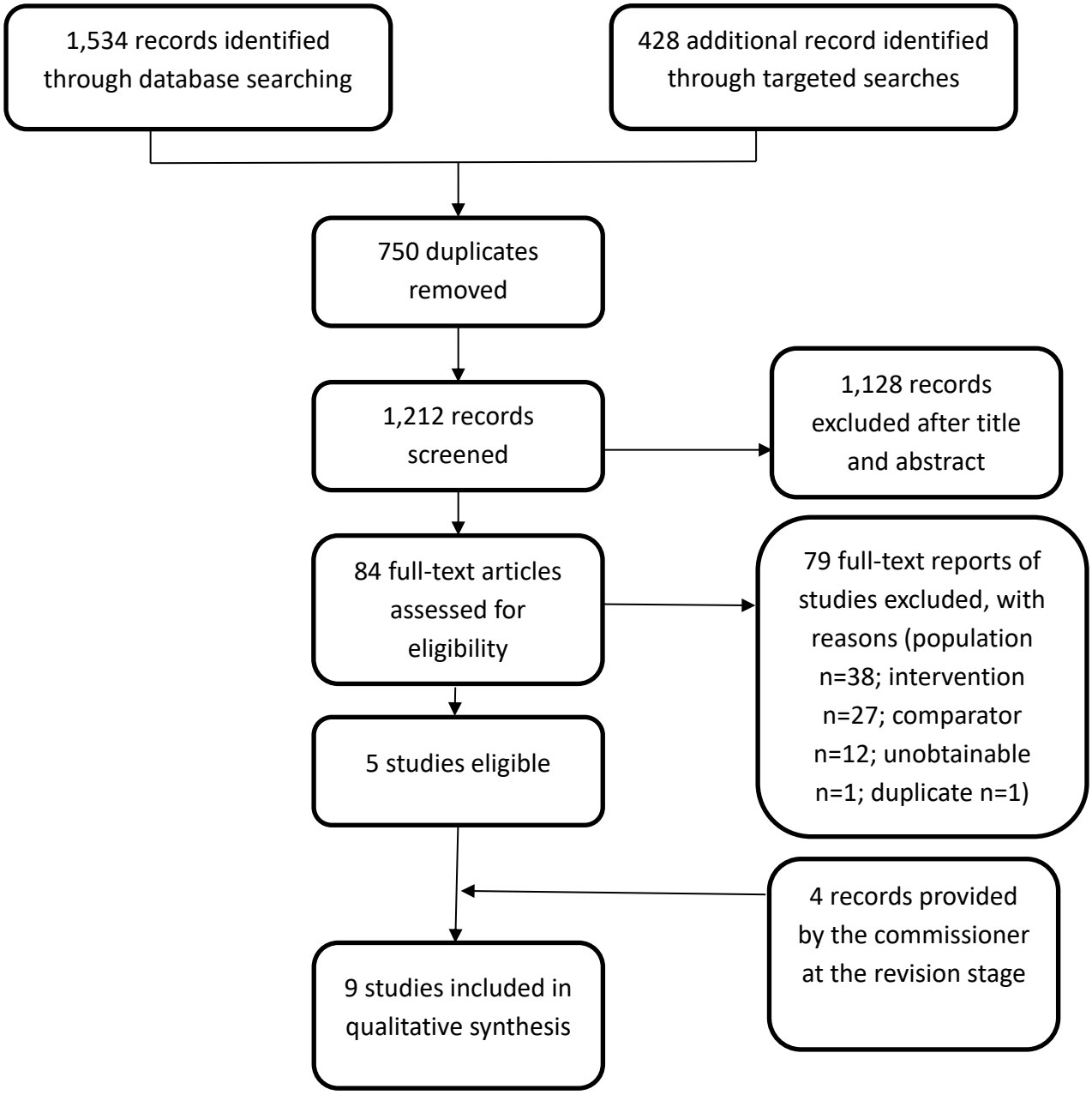
Two independent reviewers screened titles and abstracts of all records identified by the electronic searches and any disagreements were resolved through consensus. Full-text versions were obtained for all potentially eligible studies and screened by these same two reviewers independently against the pre-specified eligibility criteria. For each study, one reviewer extracted the data whereas another validated the entries. Any disagreements were settled through discussion.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Searches were conducted in January 2021 to identify all relevant SRs or CPGs. A total of 1,534 records were retrieved from the electronic literature searches; and 428 identified through targeted searches. 1,212 titles and abstracts were screened by two reviewers after removing duplicate records. After screening of 84 full-text papers, five met the inclusion criteria. Four additional studies were included at the revision stage. A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[1]

Figure 1: Study selection process



3.2 OVERVIEW OF INCLUDED STUDIES

Seven systematic reviews (SRs), and two clinical practice guidelines (CPGs) were eligible for inclusion. Table 2 below summarises the sources of evidence used to answer the respective eight FAQs. These SRs and CPGs included evidence from both randomised controlled trials (RCTs) and observational studies. Quantitative evidence from network meta-analyses (NMAs) was available to answer the FAQs 3 to 7. Qualitative evidence from two CPGs was available to answer the FAQ 1. Five SRs and meta-analyses (MAs) (head-to-head comparisons) were available to answer FAQs 3-8.

Table 2: Evidence sources

Study/year	Evidence source	Intervention	FAQ1: What does the treatment involve?	FAQ2: When is the treatment especially suitable for me?	FAQ3: Does the treatment influence the type of surgery chosen? Sphincter-preserving or not?	FAQ4: How will treatment influence my rectal tumour? - Will I respond to treatment? Is there a chance for complete remission?	FAQ5: Will treatment reduce my risk for tumour recurrence?	FAQ6: Will the treatment prolong my life?	FAQ7: Are there long-term negative effects of treatment to be expected?	FAQ8: How will treatment impact my quality of life?
AWMF 2019[2]	Guideline	NEO-RC NEO-RT SUR	✓							
Zhong 2020[3]	Systematic review and network meta-analysis	NEO-RC NEO-RT SUR			✓		✓	✓	✓	
Wo 2021[4]	Guideline	NEO-RC NEO-RT SUR	✓	✓	✓					
Ma 2017[5]	Systematic review and meta-analysis	NEO-RC NEO-RT SUR				✓		✓	✓	✓
Chen 2019[6]	Systematic review and network meta-analysis	NEO-RC NEO-RT				✓				
Caluwe 2013[7]	Systematic review and	NEO-RC NEO-RT			✓	✓	✓	✓	✓	✓

	meta-analysis	SUR								
Rahbari 2013[8]	Systematic review and meta-analysis	NEO-RC			✓	✓	✓	✓	✓	
		NEO-RT								
		SUR								
Zhou 2014[9]	Systematic review and meta-analysis	NEO-RC			✓	✓	✓	✓	✓	
		NEO-RT								
		SUR								
Loos 2013[10]	Systematic review and meta-analysis	NEO-RC								✓
		NEO-RT								
		SUR								
NEO-RC = neoadjuvant radiochemotherapy; NEO-RT = neoadjuvant radiotherapy; SUR = surgery.										

3.3 FAQ 1: WHAT DOES THE TREATMENT INVOLVE?

This section explains the three treatment options of advanced rectal carcinoma, i.e. neoadjuvant radiochemotherapy (NEO-RC), neoadjuvant short-term radiotherapy (NEO-RT) and surgery (herein also referred to low anterior resection (LAR), anterior resection (AR), total mesorectal excision (TME), intersphincteric resection (ISR), or abdominoperineal resection (APR). It is worth emphasising that the type of surgery e.g., sphincter preserving or not (the need for permanent colostoma) also depends on the location or size of the tumour as well as the existing comorbidities. These options are briefly described in Table 3.

Table 3: Description of treatments

Neoadjuvant radiochemotherapy (NEO-RC)
Neoadjuvant radiochemotherapy (NEO-RC) involves a concurrent combination of chemotherapy together with radiotherapy before surgical resection.[2] The aims of neoadjuvant chemotherapy are to make cancer cells more sensitive to radiotherapy; or to downsize/downstage i.e., (shrink the tumour size or/and stage if the tumor is bigger or less well operable). If tumours are very close to the anal sphincter (the muscle that controls defecation), NEO-RC might be reasonable as it may increase the chance to perform sphincter-preserving surgery and to reduce the risk for local recurrence. If an immediate surgery is not possible e.g., high-risk patients with cardiovascular morbidities, and concomitant use of anticoagulants, NEO-RC may also be used as a bridging strategy to gain time. It is also worth noting that some comorbidities might preclude the use of NEO-RC. A re-evaluation should take place no earlier than six weeks after completion of the NEO-RC as the effects of therapy are often apparent with a delay. This also means that the decision about a selection of surgical methods can only be made at the time of the operation i.e. after completion of NEO-RC mostly eight to 12 weeks later.[2]
Neoadjuvant radiotherapy (NEO-RT)
Neoadjuvant short-course radiation therapy (NEO-RT) is performed pre-operatively i.e. before the surgery.[2] The aims of the therapy (among others) are to achieve downsizing/downstaging if tumour is bigger or less well operable and to reduce local recurrence rates of the patient. NEO-RT might also increase the chance to perform sphincter-preserving surgery. NEO-RT typically consists of a total dose of 25 Gy administered in five fractions over the period of one week.[4] Surgery is usually done within 10 days following initiation of radiotherapy or, alternatively, 4-8 weeks later. As a part of the procedure, a pre-operative evaluation is performed which involves computer tomography scans (typically the chest, abdomen, pelvis) and magnetic resonance imaging to assess distal and local involvement, respectively.
Surgery without neoadjuvant treatment/primary resection (SUR/SA)
Surgery without neoadjuvant treatment is performed by means of low anterior resection (LAR), anterior resection (AR), total mesorectal excision (TME), intersphincteric resection (ISR), or abdominoperineal resection (APR). Surgery without neoadjuvant

treatment is usually not recommended except for a very limited group of patients. The surgical techniques differ in terms of access i.e. perineal (between the pubic arch and the tail bone), anterior (frontal) or via anus; depending on the surgeon's preference/experience. With the exception of APR (a technique designed for patients in whom sphincter preservation is not feasible which involves removal of the anus, the rectum and part of the sigmoid colon; and a permanent stoma where the end of the remaining colon is brought out on the surface of the abdomen permanently), LAR, AR, ISR and TME typically involve sphincter preservation depending on tumour size and location (except for those cancers very close to the anal sphincter). For these sphincter preserving surgeries, the most common goals include local control, long-term survival, preservation of bladder, and maintenance or improvement in quality of life. The primary goal of all surgeries is removal of the tumour and all draining lymph nodes.[2] All surgical techniques are performed by specially trained and experienced physicians under local or general anaesthesia; and the recovery time in a hospital ranges from five days to approximately a week.

3.4 FAQ 2: When is the treatment especially suitable for me?

This section explains when the treatment is especially suitable for the patient; and describes different time intervals for the NEO-RT and NEO-RC and the subsequent surgery. Only one study was included under this FAQ. Wo et al. 2021, specified the conditions under which particular interventions achieved their outcomes.[4] This was a CPG from the American Society for Radiation Oncology and included randomised and non-randomised studies in addition to SRs and meta-analyses (MAs). The authors found that the benefits of NEO-RC and NEO-RT, as well as surgery alone were conditional upon a number of factors including: confirmed radiographic diagnosis, stage of cancer, discussion with multidisciplinary team, and the need for sphincter preservation. In terms of timing, an interval of six to 11 weeks from the end of NEO-RC to surgery is recommended for patients with rectal cancer undergoing the therapy. For these cancer patients undergoing NEO-RT with no further neoadjuvant chemotherapy planned, an interval of either ≤3 days or four to eight weeks from the end of RT to surgery is recommended (an interval of four to eight weeks is preferred for patients who may benefit from tumour downstaging prior to resection). The details of their findings are summarised in Table 4 (adapted from Wo et al. 2021[4]). For SA, the German S3 Guideline recommends primary resection as an option in patients with Union Internationale Contre le Cancer (UICC) stages II and III i.e., tumours in the lower/middle third of the rectum and with questionable lymph node involvement or tumours in middle third of the rectum with only limited infiltration into the surrounding tissues and without imaging-based suspicion of lymph node metastases or extra-mural vascular invasion and with total mesorectal excision (TME) surgery.[2] For stage IV tumours, a preoperative NEO-RC should be done if the tumour is close (<1-2 mm) to the mesorectal fascia, or the tumour is very close to the anal sphincter with intended sphincter preservation.[2]

Table 4: FAQ 2 – Evidence synthesis (adapted from Wo et al. 2021[4])

Benefits of neoadjuvant RT and CRT		
Indications for neoadjuvant RT	**Strength of recommendation**	**Quality of Evidence**
For patients with rectal cancer, pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.	Strong	Moderate
For patients with stage II-III rectal cancer, neoadjuvant RT is recommended	Strong	High
For patients with stage II rectal cancer at lower risk of locoregional recurrence, omission of neoadjuvant RT is conditionally recommended after discussion with a multidisciplinary team. Implementation remark: Lower risk is defined as a cT3a/b N0 tumour that is >10 cm from the anal verge* and with mrCRM >=2 mm and no mrEMVI.	Conditional	Moderate
For patients with cT1-2N0 rectal cancer who may need an abdominoperineal resection, neoadjuvant chemoradiation is conditionally recommended to improve the chance of sphincter preservation.	Conditional	Expert opinion
For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively.	Strong	High
Indications for specific neoadjuvant regiments (RT or CRT)		
For patients with rectal cancer receiving neoadjuvant chemoradiation, conventional fractionation from 5000-5040 cGy in 25-28 fractions with concurrent chemotherapy is recommended.	Strong	High
For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended	Strong	High
For patients with rectal cancer undergoing neoadjuvant chemoradiation, only concurrent 5-fluorouracil or capecitabine is recommended with RT for radiosensitisation.	Strong	High
For patients with rectal cancer undergoing neoadjuvant therapy, chemotherapy alone (FOLFOX or CAPOX) is conditionally recommended only in the context of a clinical trial or multi institutional registry.	Conditional	Low
For patients with rectal cancer undergoing neoadjuvant therapy without tumour factors that portend increased recurrence risk, (1) chemoradiation or (2) short-course RT are recommended. Implementation remark: Risk factors for increased recurrence include cT3 tumours ≤5 cm from the anal verge or mrCRM	Strong	High

Benefits of neoadjuvant RT and CRT		
For patients with rectal cancer undergoing neoadjuvant therapy without tumour factors that portend increased recurrence risk, addition of multiagent (FOLFOX or CAPOX) chemotherapy (1) before or after chemoradiation or (2) after short-course RT is conditionally recommended	Conditional	Low
MRI = magnetic resonance imaging; T = primary tumour; N = regional lymph nodes; RT = radiotherapy; mrCRM =MRI of the pathological circumferential resection margin; mrEMVI = MRI of extramural vascular invasion; T3 = stage 3 cancer; N0 = non-sentinel lymph node metastasis; CRT = chemoradiotherapy; cGy = unit of absorbed radiation (a “gray”).		

3.5 FAQ 3: Sphincter Preservation

Three included studies found that neoadjuvant therapy was comparable to surgery alone for preserving the sphincter (Table 5).[3, 4] The SR and NMA by Zhong et al. (2020) searched three databases (MEDLINE, EMBASE and the Cochrane Library) and included RCTs only.[3] For this outcome, the authors found one randomised trial (184 patients) comparing NEO-RC with surgery alone; and reported no difference between NEO-RC and surgery alone for organ preservation odds ratio (OR) = 0.94, 95% confidence interval (CI) 0.50 to 1.77. Based on NMA, they found no difference between NEO-RT and surgery alone (OR = 0.88; 95% CI 0.46 to 1.70). The authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the levels of the evidence and it was ranked as low. In the CPG, Wo et al. 2021 identified studies of various designs (one MA, two RCTs) comparing NEO-RC with surgery alone, and also found no differences between the groups based on low quality of the evidence.[4] The SR by Zhou et al. (2014) searched four databases (PubMed, Embase, Web of Science, and the Cochrane Library).[9] They found four studies (946 patients) and reported no differences between NEO-RT and NEO-RC (65% versus 66% respectively) in sphincter preservation.[9] The SR by Rahbari et al. (2013) searched 5 databases and one trial register (the Cochrane Library, Biosis, Web of Science, Embase, ASCO Abstracts and WHO International Clinical Trials Registry) and included RCTs only. For this outcome, the authors found 5 trials that compared NEO-RC with NEO-RT and reported no between group differences (OR = 1.04; 95% CI 0.87 to 1.25) based on moderate quality evidence.[8] It is worth reiterating that depending on tumour size and location most surgical techniques such as LAR, AR, ISR and TME involve sphincter preservation. For the cancers very close to the anal sphincter, preoperative NEO-RC or NEO-RT might increase the chance to perform these sphincter-preserving surgeries.[2]

Table 5: FAQ 3 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with (95% CIs)	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Sphincter preservation							
Zhong 2020[3]	0*	Minimum 3 years	NEO-RT (inestimable)	SA (inestimable)	OR 0.88 (95% CI 0.46 to 1.70)	Low (unclear risk of bias, imprecision)	No difference shown ⇔
Zhong 2020[3]	1 (RCT)	Minimum 3 years	NEO-RC (inestimable)	SA (inestimable)	OR 0.94 (95% CI 0.50 to 1.77)	Low (f unclear risk of bias, imprecision)	No difference shown ⇔
Wo 2021[4]	3 (2 RCTs+1 MA)	NR	NEO-RC (inestimable)	SA (inestimable)	NR	Very low (very low quality data)	No difference shown ⇔
Caluwe 2013[7]	5 RCTs	NR	NEO-RC 583/1,157 (50.3%)	NEO-RT 553/1,145 (48.2%)	OR 1.09 (95% CI 0.92 to 1.30)	Moderate (moderate quality data)	No difference shown ⇔
Zhou 2014[9]	3 RCTs, 2 non-RCTs	NR	NEO-RC 317/483 (66%)	NEO-RT 300/463 (65%)	RR = 1.00 (95%CI 0.91 to 1.09)	Low (low quality data)	No difference shown ⇔
Rahbari 2013[8]	5 trials	NR	NEO-RC (inestimable)	NEO-RT (inestimable)	OR 1.04 (95% CI 0.87 to 1.25)	Moderate (moderate quality data)	No difference shown ⇔

* estimate from network meta-analysis
CI = confidence interval; MA = meta-analysis; NEO-RC = neoadjuvant radiochemotherapy; NEO-RT = neoadjuvant radiotherapy; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; SA = surgery alone.

3.6 FAQs 4&5: How will treatment influence my rectal tumour? Is there a chance for complete remission; Will treatment reduce my risk for tumour recurrence?

This section explains whether specific type of neoadjuvant therapy, i.e. NEO-RT or NEO-RC improves chances for local remission. Five oncological outcomes are presented i.e. local recurrence-free survival, local control, local recurrence, pathological complete response, or metastases when compared with surgery alone. Five included studies answered these questions with no definitive evidence.[3, 5, 7-9] All studies showed benefit of NEO-RC or/and NEO-RT in improving local recurrence-free survival, local control, local recurrence, pathological complete response when compared with surgery alone (details below and in Table 6).

3.6.1. Local recurrence-free survival

One included study found that both NEO-RT and NEO-RC might improve recurrence-free survival compared with surgery alone.[5] The study by Ma et al. (2017) searched PubMed, Embase and Web of Science databases. They pooled data from both controlled and uncontrolled studies; and reported that both NEO-RT and NEO-RC improved local recurrence-free survival (hazard ratio (HR) = 0.53; 95% CI 0.46 to 0.62; n=19 studies and HR 0.63 95% CI 0.42 to 0.97; n=15 studies, respectively). These benefits were observed in all subgroups (regardless of age, and different neoadjuvant regimes).[5] The quality of the underpinning data was moderate for both comparisons (see Table 6).

3.6.2. Local control

The SR by Rahbari et al. (2013) reported that NEO-RT improved local control when compared with surgery alone (HR = 0.59; 95% CI 0.48 to 0.72; 10 studies) based on moderate quality evidence[8]

3.6.3 Local recurrence

One included study indicated that NEO-RC (but not NEO-RT) likely reduces the risk of tumour recurrence when compared with surgery alone (FAQ 5).[3] For this outcome/FAQ, the NMA by Zhong et al. (2020) found that compared with surgery alone (SA), NEO-RT reduces the chances of local recurrence (OR = 0.44; 95% CI 0.37 to 0.51), based on high quality evidence.[3] However, compared with SA, NEO-RC showed no difference in reducing the risk of local recurrence (OR = 1.05; 95% CI 0.25 to 4.30), based on low quality evidence (see Table 6).

3.6.4. Pathological complete response

The SR by Zhou et al. (2014) included seven studies (1,165 patients) and found no difference between NEO-RT and NEO-RC in reducing the risk of local recurrence (8.6% versus 10% respectively).[9] However there was increased pathological complete response (pCR) following NEO-RC (11.2%) compared with NEO-RT (1.23%) (7 studies with 1,197 participants).

3.6.5 Metastases

For metastases, the NMA by Zhong et al. (2020) found no differences between either NEO-RT or NEO-RC when compared with surgery alone (OR = 0.87; 95% CI 0.73 to 1.05 and OR 0.76; 95% CI 0.30 to 1.90, respectively) based on low quality evidence.[3] The SR by Zhou et al. (2014)

included five studies (789 patients) and found no differences between NEO-RT compared with NEO-RC in reducing metastasis rate (27% versus 29% respectively) based on moderate quality evidence.[9]

Table 6: FAQs 4&5 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Local recurrence-free survival							
Ma 2017[5]	19 (cohort and controlled studies)	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.53 (95% CI 0.46 to 0.62)	Moderate (mixed quality data)	Benefit of NEO-RT ⇗ but data of moderate quality
Ma 2017[5]	15 (cohort and controlled studies)	NR	NEO-RC (inestimable)	SA (inestimable)	HR 0.63 (95% CI 0.42 to 0.97)	Moderate (mixed quality data)	Benefit of NEO-RC ⇗ but data of moderate quality
Local control							
Rahbari 2013[8]	10 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.59 (95% CI 0.48 to 0.72)	Moderate (mixed quality data)	Benefit of NEO-RC ⇗ but data of moderate quality
Local recurrence							
Caluwe 2013[7]	3 trials	5 years	NEO-RC 71/754 (9.4%)	NEO-RT 122/740 (16.4%)	OR 0.53 (95% CI 0.39 to 0.72)	Low (data of low quality, inconsistency)	Benefit of NEO-RC ⇗ but data of low quality
Rahbari 2013[8]	10 trials	NR	NEO-RC (inestimable)	SA (inestimable)	HR 0.59 (95% CI 0.48 to 0.72)	Moderate (data of moderate quality, inconsistency)	Difference in favour of NEO-RC; data of moderate quality ⇗
Zhong 2020[3]	11 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	OR 0.44 (95% CI 0.37 to 0.51)	High (data of high quality)*	Difference in favour of NEO-RT; data of high quality ⇧

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Zhong 2020[3]	1 RCT (184 patients)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 1.05 (95% CI 0.25 to 4.30)	Low (data of low quality, imprecision)	No difference shown ⇔
Zhou 2014[9]	3 RCTs, 4 non-RCTs	NR	NEO-RT 52/602 (8.6%)	NEO-RC 57/563 (10%)	RR 0.83 (95%CI 0.58 to 1.18)	Moderate (moderate quality data)	No difference shown ⇔
Pathological complete response							
Caluwe 2013[7]	5 trials	NR	NEO-RC 135/1,142 (11.8%)	NEO-RT 40/1,142 (3.5%)	OR 3.52 (95% CI 2.12 to 5.84)	Low (data of low quality, imprecision)	Benefit of NEO-RC ⇗ but data of low quality
Zhou 2014[9]	3 RCTs, 4 non-RCTs	NR	NEO-RT 7/565 (1.23%)	NEO-RC 71/632 (11.2%)	RR 0.15 (95%CI 0.08 to 0.28)	Moderate (moderate quality data)	Benefit of NEO-RC ⇗ but data of moderate quality
Metastases							
Zhong 2020[3]	8 trials	NR	NEO-RT (inestimable)	SA (inestimable)	OR 0.87 (95% CI 0.73 to 1.05)	Low (data of low quality)	No difference shown ⇔
Zhong 2020[3]	1 trial	NR	NEO-RC (inestimable)	SA (inestimable)	OR 0.76 (95% CI 0.30 to 1.90)	Low (data of low quality)	No difference shown ⇔
Zhou 2014[9]	5 trials	NR	NEO-RT 108/398 (27%)	NEO-RC 114/391 (29%)	RR 0.95 (95%CI (0.76 to 1.18)	Moderate (some methodological problems)	No difference shown ⇔

* = data quality judged by Zhong et al. (23 randomised controlled studies at a low risk of bias); CI = confidence interval; NEO-RC = neoadjuvant radiochemotherapy; NEO-RT = neoadjuvant radiotherapy; NR = not reported; OR = odds ratio; RR = risk ratio; SA = surgery alone.

3.7 FAQ 6: WILL THE TREATMENT PROLONG MY LIFE?

This section explains whether specific type of neoadjuvant therapy, i.e. NEO-RT or NEO-RC extends life-expectancy. Three oncological outcomes are presented i.e. overall survival, disease-free survival, and metastasis-free survival when compared with surgery alone. Five included studies answered this question with no definitive evidence.[3, 5, 7-9] See Table 7 for details. There was not a large between NEO-RT or NEO-RC and surgery alone, although NEO-RT had a small benefit for some outcomes (details below and in Table 7).

3.7.1 Overall survival (OS)

For this outcome/FAQ, the SR by Caluwe et al. (2020) found that compared with NEO-RT, NEO-RT did not reduce mortality at 5-years follow-up (OR = 1.05; 95% CI 0.88 to 1.27) based on moderate quality evidence.[7] Ma et al. (2017) found that when compared with surgery alone, NEO-RT may slightly reduce mortality (HR = 0.93; 95% CI 0.86 to 1.01).[5] However, there were no differences between either NEO-RC and surgery alone in reducing mortality (HR = 0.83; 95% CI 0.62 to 1.11) based on low quality evidence.[5] The SR by Rahbari et al. (2013) reported there was a slightly reduced mortality in the NEO-RT group compared with SA (HR = 0.93; 95% CI 0.85 to 1.00; 12 studies); and no differences between NEO-RC and NEO-RT (HR = 1.03; 95% CI 0.89 to 1.19) based on moderate quality evidence.[8] The NMA by Zhong et al. (2020) found that compared with SA, NEO-RT reduces mortality (HR = 0.89; 95% CI 0.83 to 0.96) based on moderate quality evidence.[3] However, compared with surgery alone, NEO-RC showed no difference in reducing mortality (HR = 1.34; 95% CI 0.43 to 4.21) based on low quality evidence (see Table 7).[3] The SR by Zhou et al. (2014) included eight studies (1,262 patients) and found no difference between NEO-RT and NEO-RC (26% versus 31% respectively) based on moderate quality evidence.[9]

3.7.2 Disease-free survival (DFS)

For this outcome, the SR by Caluwe et al. (2013) no difference between NEO-RC and NEO-RT (OR = 0.90; 95% CI 0.74 to 1.09) based on moderate-quality randomised trials. [7] In their SR, Ma et al. (2017),[5] favourable findings for NEO-RT and no differences between NEO-RC when compared with surgery in DFS were identified (HR 0.87; 95% CI 0.77 to 0.98) and (HR = 0.98; 95% CI 0.66 to 1.45) respectively.[5] The SR by Rahbari et al. (2013) reported there was an increased DFS in the NEO-RT group compared with SA (HR = 0.85 95% CI 0.75 to 0.97; 4 studies); and no differences between NEO-RC and NEO-RT (HR = 0.95; 95% 0.84 to 1.07) based on moderate quality evidence.[8] In a NMA, Zhong et al. (2020) found that compared with SA, NEO-RT may increase disease-free survival (DFS) (HR = 0.80; 95% CI 0.63 to 1.02) based on low quality evidence.[3] However, compared with surgery alone, NEO-RC showed no difference in DFS (HR = 1.48; 95% CI 0.34 to 6.52).[3] The SR by Zhou et al. (2014) included six studies (1,105 patients) and found increased DFS following NEO-RT compared with NEO-RC (36% versus 43% respectively) based on moderate quality evidence.[9]

3.7.3 Metastasis-free survival

Similarly, no differences between either NEO-RT or NEO-RC when compared with surgery alone were found for metastasis-free survival in Ma et al. (2017) (HR = 1.05; 95% CI 0.85 to

1.28 and HR = 0.97, 95% CI 0.76 to 1.24, respectively).[5] The quality of the evidence was low for this outcome.

Table 7: FAQ 6 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Overall survival							
Caluwe 2013[7]	3 RCTs	5 years	NEO-RC 363/1007 (36%)	NEO-RT 346/993 (34.8%)	OR 1.05 (95% CI 0.88 to 1.27)	Moderate (some methodological problems with included trials)	No difference shown ⇔
Ma 2017[5]	22 (cohort and controlled studies)	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.93 (95% CI 0.86 to 1.01)	Low (data of low quality according to Newcastle-Ottawa scale)	No difference shown ⇔
Ma 2017[5]	14 (cohort studies)	NR	NEO-RC (inestimable)	SA (inestimable)	HR 0.83 (95% CI 0.62 to 1.11)	Low (data of low quality)	No difference shown ⇔
Rahbari 2013[8]	12 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.93 (95% CI 0.85 to 1.00)	Moderate (some methodological problems with included trials)	Difference in favour of NEO-RT; data of moderate quality ⇗
Rahbari 2013[8]	5 RCTs	NR	NEO-RC (inestimable)	NEO-RT (inestimable)	HR 1.03 (95% CI 0.89 to 1.19)	Moderate (some methodological problems with included trials)	No difference shown ⇔
Zhong 2020[3]	13 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.89 (95% CI 0.83 to 0.96)	Moderate (data of high quality, but indirect)*	Difference in favour of NEO-RT; data of high quality ⇧

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Zhong 2020[3]	1 RCT	NR	NEO-RC (inestimable)	SA (inestimable)	HR 1.34 (95% CI 0.43 to 4.21)	Low (data of low quality and imprecision)	No difference shown ⇔
Zhou 2014[9]	3 RCTs, 5 non-RCTs	NR	NEO-RT 176/665 (26%)	NEO-RC 183/597 (31%)	RR 0.89 (95% CI 0.75 to 1.06)	Moderate (moderate quality data)	No difference shown ⇔
Disease-free survival							
Caluwe 2013[7]	2 RCTs	5 years	NEO-RC 374/881 (42.4%)	NEO-RT 393/872 (45%)	OR 0.90 (95% CI 0.74 to 1.09)	moderate (methodological problems with included studies)	No difference shown ⇔
Ma 2017[5]	8 (cohort and controlled studies)	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.87 (95% CI 0.77 to 0.98)	Low (data of low quality)	Difference in favour of NEO-RT but data of low quality ⇗
Ma 2017[5]	10 (cohort studies)	NR	NEO-RC (inestimable)	SA (inestimable)	HR 0.98 (95% CI 0.66 to 1.45)	Low (data of low quality)	No difference shown ⇔
Rahbari 2013[8]	4 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.85 (95% CI 0.75 to 0.97)	Moderate (moderate quality data)	Difference in favour of NEO-RT; data of moderate quality ⇗
Rahbari 2013[8]	5 RCTs	NR	NEO-RC	NEO-RT	HR 0.95 (95% 0.84 to 1.07)	Moderate (moderate quality data)	No difference shown ⇔

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Zhong 2020[3]	4 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	HR 0.80 (95% CI 0.63 to 1.02)	Low (data of low quality)	Difference in favour** of NEO-RT; data of low quality ⇗
Zhong 2020[3]	1 RCT	NR	NEO-RC (inestimable)	SA (inestimable)	HR 1.48 (95% CI 0.34 to 6.52)	Low (data of low quality and imprecision)	No difference shown ⇔
Zhou 2014[9]	3 RCTs, 3 non-RCTs	NR	NEO-RT 206/563 (36%)	NEO-RC 231/542 (43%)	RR 0.86 (95%CI 0.74 to 0.99)	Moderate (moderate quality data)	Difference in favour of NEO-RT ⇗ data of moderate quality
Metastasis-free survival							
Ma 2017[5]	11 (cohort and controlled studies)	NR	NEO-RT (inestimable)	SA (inestimable)	HR 1.05 (95% CI 0.85 to 1.28)	Low (data of low quality)	No difference shown ⇔
Ma 2017[5]	7 (cohort studies)	NR	NEO-RC (inestimable)	SA (inestimable)	HR 0.97 (95% CI 0.76 to 1.24)	Low (data of low quality)	No difference shown ⇔

* = data quality judged by Zhong et al. (23 randomised controlled studies at a low risk of bias, however they were old and populations/concomitant care have evolved); ** = based on both the Ma 2017 and Zhong (2020) studies reporting the same outcome; CI = confidence interval; HR = hazard ratio; NEO-RC = neoadjuvant radiochemotherapy; NEO-RT = neoadjuvant radiotherapy; NR = not reported; RCT = randomised controlled trial.

3.8 FAQ 7: ARE COMPLICATIONS/NEGATIVE EFFECTS TO BE EXPECTED FROM TREATMENT?

Two studies investigated whether NEO-RT or NEO-RC causes adverse events (FAQ 7), [3, 5] and none found that the neoadjuvant therapies caused more adverse events than surgery alone – see Tables 8 and 9.

3.8.1 30-days mortality

The SR by Rahbari et al. (2013) reported there was an increased risk of perioperative mortality in the NEO-RT group compared with SA (HR = 1.48; 95% CI 1.08 to 2.03); and no differences between NEO-RC and NEO-RT (OR = 1.47; 95% CI 0.83 to 2.61) based on moderate quality evidence.[8] None of the other included studies found differences between NEO-RT or NEO-RC when compared with surgery alone, with all data being of moderate to low quality. Caluwe et al. (2013) found in their SR found no difference between NEO-RC and NEO-RT (OR = 1.48; 95% CI 0.83 to 2.63, moderate quality data). [7] Zhong et al. (2020) found no differences between either NEO-RT or NEO-RC when compared with surgery alone in their NMA (OR = 1.38; 95% CI 0.89 to 2.12 and OR = 2.20; 95% CI 0.68 to 6.40, respectively, moderate quality data).[3] Table 8 contains additional details.

3.8.2 Anastomotic leakage

No differences between NEO-RT when compared with surgery alone were found for anastomotic leakage (a leak of luminal contents from a surgical connection of parts of colon) in one study based on moderate quality evidence (OR = 1.12; 95% CI 0.75 to 1.67), see Table 8.[3, 5] However, NEO-RC may reduce the risk of anastomotic leakage when compared with surgery alone (OR = 0.24; 95% CI 0.05 to 1.18).[3] The SR by Rahbari et al. (2013) reported no differences between NEO-RC and SA (HR = 0.96; 95% CI 0.58 to 1.60) based on moderate quality evidence.[8] Caluwe et al.'s SR found no difference between NEO-RC and NEO-RT for this outcome (OR = 1.07; 95% CI 0.62 to 1.84).[7]

3.8.3 Toxicity

The SR by Zhou et al. (2014) included three studies (450 patients) and found that compared with NEO-RC, NEO-RT appeared to have a lower frequency of grade 1-4 acute toxicity (65% versus 3% respectively).[9] The SR by Rahbari et al. (2013) reported there was an increased risk of acute (grade III-IV) toxicity in the NEO-RC group compared with NEO-RT (OR = 4.10; 95% CI 1.68 to 10.0) based on moderate quality evidence.[8] The SR by Caluwe reported less toxicity caused by NEO-RT compared with NEO-RC (OR = 4.1; 95% CI 1.68 to 10.0) based on moderate quality evidence. [7]

3.8.4 Morbidity

The SR by Rahbari et al. (2013) reported there was an increased risk of perioperative mortality in the NEO-RT group compared with SA (HR = 1.25; 95% CI 1.02 to 1.54); and no differences between NEO-RC and NEO-RT (OR = 0.82; 95% CI 0.67 to 1.00) based on moderate quality evidence.[8] The SR by Caluwe et al (2013) did not find a difference in morbidity between NEO-RC and NEO-RT (OR = 0.82; 95% CI 0.67 to 1.0) based on moderate quality data.

3.8.5 Other

Two reviews compared surgery alone with NEO-RC for several additional potential harms. Ma (2017)[5] identified (range 3 to 6) nonrandomised studies of low quality, while the SR and NMA by Loos et al. (2013) searched three databases (MEDLINE, EMBASE and the Cochrane Library) and included both RCTs and non-RCTs.[10] For stool or urinary incontinence and erectile dysfunction, the authors found (range 3 to 4) studies comparing NEO-RC with SA. Surgery alone (SA) seemed to lead to lower rates of anorectal urgency, stool incontinence, erectile dysfunction, and sexual dysfunction compared with NEO-RC. The biggest difference was found for sexual dysfunction, where NEO-RC was five times more likely to cause it compared with SA (OR = 5.15; 95% CI 0.67 to 39.47) (see Table 9). One review of the prevalence of low anterior resection syndrome (LARS) searched three databases for relevant English language studies. The authors found that serious LARS was prevalent in 41% of patients (see Table 9).[11] This review also states that "A low anastomotic height or history of radiotherapy are major risk factors for LARS."

Table 8: FAQ 7 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
30 days mortality								
Caluwe 2013[7]		5 RCTs	NR	NEO-RC 31/1,168 (2.6%)	NEO-RT 21/1,154 (1.8%)	OR 1.48 (95% CI 0.83 to 2.63)	Low (data of low quality)	No difference shown ⇔
Rahbari 2013[8]		15 RCTs	NR	NEO-RC 198/3946 (5%)	SA 136/4001 (3.4%)	HR 1.48 (95% CI 1.08 to 2.03)	Moderate (data of moderate quality)	Difference in favour of SA but moderate quality of data⇗
Rahbari 2013[8]		4 RCTs	NR	NEO-RC (inestimable)	NEO-RT (inestimable)	OR 1.47 (95% CI 0.83 to 2.61)	Moderate (data of moderate quality)	No difference shown ⇔
Zhong 2020[3]		13 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	OR 1.38 (95% CI 0.89 to 2.12)	Moderate (data of moderate quality)	No difference shown ⇔
Zhong 2020[3]		0*	NR	NEO-RC (inestimable)	SA (inestimable)	OR 2.20 (95% CI 0.68 to 6.40)*	Moderate (data of moderate quality)	No difference shown ⇔
Anastomotic leakage								
Caluwe 2013[7]		4 RCTs	NR	NEO-RC 31/588 (5.2%)	NEO-RT 27/563 (4.7%)	OR 1.07 (95% CI 0.62 to 1.84)	Low (data of low quality)	No difference shown ⇔

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Rahbari 2013[8]		9 RCTs	NR	NEO-RC (inestimable)	SA (inestimable)	HR 0.96 (95% CI 0.58 to 1.60)	Moderate (data of moderate quality)	No difference shown ⇔
Zhong 2020[3]		5 RCTs	NR	NEO-RT (inestimable)	SA (inestimable)	OR 1.12 (95% CI 0.75 to 1.67)	Moderate (data of moderate quality)	No difference shown ⇔
Zhong 2020[3]		1 RCTs	NR	NEO-RC (inestimable)	SA (inestimable)	OR 0.24 (95% CI 0.05 to 1.18)	Low (data of low quality; imprecision)	Difference in favour of NEO-RC but imprecise data of low quality⇗
Toxicity								
Zhou 2014[9]		3 studies (1 RCT, 2 non-RCT)	NR	NEO-RT 5/165 (3%)	NEO-RC 185/285 (65%)	RR 0.07 (95%CI 0.00 to 1.87)	Low (data of low quality; inconsistency and imprecision)	Difference in favour of NEO-RT but imprecise data of low quality⇗
Rahbari 2013[8]		NR	NR	NEO-RT (inestimable)	NEO-RC (inestimable)	OR 4.10 (95% CI 1.68 to 10.0)	Moderate (data of moderate quality; inconsistency)	Difference in favour of NEO-RT moderate quality of data⇗
Caluwe 2013[7]		3 RCTs	NR	NEO-RC 151/1015 (14.9%)	NEO-RT 52/1017 (5.1%)	OR 4.1 (95% CI 1.68 to 10.0)	Moderate (some methodological problems with included studies)	Difference in favour of NEO-RT moderate quality of data⇗
Morbidity (unspecified)								
Caluwe 2013[7]		4 RCTs	NR	NEO-RC 229/1044	NEO-RT 263/1033	OR 0.82 (95% CI 0.67 to 1.0)	Moderate (some methodological	No difference shown ⇔

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
				(21.9%)	(25.5%)		problems with included studies)	
Rahbari 2013[8]		7 RCTs	NR	NEO-RC (inestimable)	SA (inestimable)	HR 1.25 (95% CI 1.02 to 1.54)	Moderate (some methodological problems with included studies)	Difference in favour of SA moderate quality of data⇗
Rahbari 2013[8]		5 RCTs	NR	NEO-RC (inestimable)	NEO-RT (inestimable)	OR 0.82 (95% CI 0.67 to 1.00)	Moderate (data of moderate quality)	No difference shown ⇔

* estimate from network meta-analysis

CI = confidence interval; HR = hazard ratio; NEO-RC = neoadjuvant radiochemotherapy; NEO-RT = neoadjuvant radiotherapy; NR = not reported; OR = odds ratio; RCT = randomised controlled trial;

Table 9: FAQ 7 – Evidence synthesis

Outcome: Quality of life (domain)	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs, e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Low Anterior Resection Syndrome (LARS)	Croese [11]	11 nonrandomised studies	12 months	Major LARS 41% (95% CI 0.34 to 0.48)		Inestimable	Low (unclear risk of bias and indirectness)	
Anorectal: urgency	Ma 2017[5]	3 studies (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 2.40 (95% CI 1.08 to 5.32)	Low (data of low quality, imprecision)	Difference in favour of SA but data of low quality ⇗
Anorectal: stool incontinence	Ma 2017[5]	4 studies (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 1.81 (95% CI 1.28 to 2.56)	Low (data of low quality, imprecision)	Difference in favour of SA but data of low quality ⇗
Anorectal: stool incontinence	Loos 2013[10]	3 RCTs	NR	NEO-RC 128/230 (55.6%)	SA 83/258 (32.1%)	RR 1.67 (95 % CI 1.36 to 2.05)	Low (data of low quality, imprecision)	Difference in favour of SA but data of low quality ⇗
Gastrointestinal: constipation	Ma 2017[5]	3 studies (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 1.47 (95% CI 0.73 to 2.86)	Low (data of low quality, imprecision)	No difference shown ⇔
Gastrointestinal: diarrhoea	Ma 2017[5]	5 studies (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 1.06 (95% CI 0.35 to 3.23)	Low (data of low quality, imprecision)	No difference shown ⇔

Outcome: Quality of life (domain)	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs, e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Urinary: incontinence	Ma 2017[5]	6 studies (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 1.33 (95% CI 0.79 to 2.24)	Low (data of low quality, imprecision)	No difference shown ⇔
Urinary: incontinence	Loos 2013[10]	4 RCTs	NR	NEO-RC125/347 (36%)	SA 117/358 (32.6%)	RR 1.05 (95 % CI 0.67 to 1.65)	Low (data of low quality, imprecision)	No difference shown ⇔
Urinary: dysfunction	Ma 2017[5]	3 studies (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 0.84 (95% CI 0.58 to 1.23)	Low (data of low quality, imprecision)	No difference shown ⇔
Erectile dysfunction	Ma 2017[5]	4 nonrandomised studies	NR	NEO-RC	SA (inestimable)	OR 2.25 (95% CI 1.51 to 3.35)	Low (data of low quality, imprecision)	Difference in favour of SA but data of low quality ⇗
Erectile dysfunction	Loos 2013[10]	3 RCTs	NR	NEO-RC 66/102 (64.7%)	SA 29/66 (43.9%)	RR 1.41 (95 % CI 0.74 to 2.72)	Low (data of low quality, imprecision)	No difference shown ⇔
Sexual dysfunction	Ma 2017[5]	3 (mixed randomised, nonrandomised)	NR	NEO-RC (inestimable)	SA (inestimable)	OR 5.15 (95% CI 0.67 to 39.47)	Low (data of low quality, imprecision)	Difference in favour of SA but very imprecise data of low quality ⇗

CI = confidence interval; NEO-RC = neoadjuvant radiochemotherapy; NEO-RT = neoadjuvant radiotherapy; NR = not reported.

3.9 FAQ 8: How will treatment impact my quality of life?

None of the studies measured quality of life directly using standard HRQOL scales, and Caluwe (2013) noted that future trials should assess quality of life directly.[7] However, many of the adverse events (see FAQ 7) are likely to impact quality of life.

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

In general, the certainty of the evidence varied from very low to high; findings were inconsistent for some (but not all) FAQs/outcomes. For instance, findings consistently showed no differences between NEO-RC or NEO-RT and surgery alone for organ preservation based on low quality of the evidence. The main reasons for downgrading were unclear quality of data, inconsistency and imprecision.

Findings were consistent for FAQ 4. Ma et al. (2017) reported that both neoadjuvant therapies i.e., NEO-RT and NEO-RC improved local recurrence-free survival based on moderate quality of the evidence from both cohort and controlled studies.[5]

Findings were inconsistent for FAQ 5. For example, based on high quality evidence, when compared with surgery alone, NEO-RT reduces the chances of local recurrence.[3] However, the same study found no differences between NEO-RC compared with surgery in reducing the local recurrence based on low quality of the evidence from one trial. Based on our clinical experts' suggestion, we further looked into the Stockholm III study following completion of this evidence report [12, 13]. Stockholm III - among other long-term NEO RT interventions - provides comparative evidence for two of the interventions included also in our PICO: short-term radiotherapy followed by immediate surgery (within one week) or followed by delayed surgery 4-8 weeks later. In Stockholm III, 385 patients in total were recruited and randomised; 129 in the short course radiotherapy + surgery, 128 in the short-course radiotherapy + delayed surgery, and 128 to long-course radiotherapy + delayed surgery in a three-arm randomisation; and in addition: 455 patients in a two-arm randomisation, of whom 228 were randomly assigned to short-course radiotherapy + immediate surgery and 227 to short-course radiotherapy + delayed surgery. For the latter two therapy arms the following results were reported:[12] 2 out of 100 patients suffered local recurrence of cancer in the 5 years trial period following short-term radiotherapy plus surgery compared to 3 of 100 in the short-course delayed surgery group. No significant difference in recurrence rates of short-course vs. short-course with delayed surgery (HR = 1·44 [90% CI 0·41–5·11; p=0.48] was observed overall. However, postoperative complications (in about 50 of 100 in the immediate surgery versus in about 40 of 100 in the delayed surgery group) seemed – in a separate pooled analysis comparing these two groups, slightly lower in the delayed surgery group (OR 0·61 [95% CI 0·45–0·83] p=0·001). A second publication of the Stockholm III trial [13] also reported a possible complete response (pCR) of less than 1 patient of 100 in the short course radiotherapy group versus about 10 of 100 in the short course delayed surgery group over the 5-years follow-up period, indicating an advantage for delaying surgery following radiotherapy.

Similarly, findings were consistent for overall survival/FAQ 6. When compared with surgery alone, NEO-RT reduces mortality, based on variable low to high quality evidence.[3, 5] However, these same two studies found no differences for NEO-RC when compared with surgery alone in reducing mortality based on low quality of the evidence.[3, 5]

Analogically, when compared with surgery alone, NEO-RT may increase DFS, based on low quality evidence from two studies.[3, 5] These same two studies found no differences for NEO-RC when compared with SA in DFS based on low quality of the evidence.[3, 5]

Findings were consistent for FAQ 7 – none of the regimes showed differences in reducing metastasis-free survival, metastases, or 30-days mortality when compared with surgery.[3, 5] Findings were rather inconsistent for anastomotic leakage. The certainty of the evidence varied from low to moderate for this FAQ 7 (predominantly low). No differences were found between NEO-RC and surgery for a number of additional adverse events: urinary dysfunction, urinary incontinence, gastrointestinal diarrhoea, or constipation.[5] However, based on low certainty evidence, Ma et al. (2017) found that NEO-RC probably worsens anorectal urgency, stool incontinence, sexual dysfunction and erectile dysfunction when compared with surgery alone.[5] The length of follow-up was poorly reported in the included studies. One of the reviews found that the prevalence of LARS was quite high in all treatment groups.[11]

None of the studies investigated quality of life (FAQ 8).

4.2 Strength, limitations and uncertainties

This report has several strengths including comprehensive searches, as well as coverage of a broad range of FAQs/outcomes of interest. Evidence from high quality SRs and CPGs was used when developing this report. For two outcomes, i.e. local recurrence and overall survival, data were of high quality, hence certainty of the estimates and heterogeneity in study results was also high.

This report also has several limitations. For instance, there was an unequal distribution of data for FAQs 2 to 5 compared with FAQs 6 to 8. None of the studies included direct measures of health-related quality of life. Additionally, heterogeneity of populations, diversity of neoadjuvant therapies, comparators, study designs and time horizons further limit applicability of the findings. Total neoadjuvant therapy (TNT), which incorporates chemotherapy with chemoradiotherapy as well as other systemic therapies without immediate surgery should be mentioned here as a relevant option for the future.[14]

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APPENDIX 1: SEARCH STRATEGIES

SR/Guidelines searches

Database	Dates	Results
CDSR & CDSR Protocols	2015 – 2021/02/Iss1	61
DARE	2015 – 2015/03	0
HTA	2015 – 2018/03	3
INAHTA	2015 – 2021/01/28	13
KSR Evidence	2015 – 2021/01/27	496
Epistemonikos	2015 - 2021/01/27	590
NHS Evidence	2015 - 2021/01/26	215
NICE	2015 - 2021/01/27	13
GIN	2015 - 2021/01/28	4
ECRI	2015 - 2021/01/26	13
TRIP	2015 - 2021/01/26	126
Total		**1534**

SDM database searches

Database	Dates	Results
Embase	2016-2021-01/27	241
MEDLINE & PreMedline	2016-2021/01/27	187
Total		**428**

SR/Guidelines searches

Cochrane Database of Systematic Reviews (CDSR): up to 2021/01/Iss1
Searched 26.1.21

#1 MeSH descriptor: [Rectal Neoplasms] explode all trees 1830
#2 ((rectal* or rectum* or anal or anus) NEAR/3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*)) 5516
#3 #1 or #2 5516
#4 MeSH descriptor: [General Surgery] explode all trees 353
#5 (surger* or surgical* or resect* or excision* or operat* or preoper* or presurg* or neoadjuvant or TNT) 321233
#6 #4 or #5 321233
#7 #3 and #6 with Cochrane Library publication date Between Jan 2015 and Feb 2021 2678
CDSR retrieved 52 records
CDSR protocols retrieved 9 records

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03
Health Technology Assessment (HTA) database (CRD): up to 2018/03
http://www.crd.york.ac.uk/CRDWeb/
Searched 26.1.21

1 MeSH DESCRIPTOR Rectal Neoplasms EXPLODE ALL TREES 230
2 (((rectal* or rectum* or anal or anus) NEAR3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*))) 351
3 #1 OR #2 351
4 MeSH DESCRIPTOR General Surgery EXPLODE ALL TREES 61
5 ((surger* or surgical* or resect* or excision* or operat* or preoper* or presurg* or neoadjuvant or TNT)) 19437
6 #4 OR #5 19437
7 #3 AND #6 265
8 (#7) IN DARE FROM 2015 TO 2021 0
9 (#7) IN HTA FROM 2015 TO 2021 3

INAHTA (https://database.inahta.org/): up to 2021/01/28
Searched: 28.1.21

((Rectal Neoplasms)[mh] OR (((rectal* or rectum* or anal or anus) AND (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*))) FROM 2015 TO 2021) AND (and (surger* or surgical* or neoadjuvant or preoper* or presurg*))
13 results

KSR Evidence (www.ksrevidence.com): up to 21/01/27
Searched: 27.1.21

1 rectal* or rectum* or anal or anus in Title or Abstract 1277 results
2 cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion* in Title or Abstract 28022 results
3 #1 and #2 in Title or Abstract 780 results
4 surger* or surgical* or resect* or excision* or operat* or preoper* or presurg* or neoadjuvant in Title or Abstract 28695 results
5 #3 and #4 in Title or Abstract 496 results

Filtered by: PUBLICATION DATE 2021, 2020, 2019, 2018, 2017, 2016, 2015

Epistemonikos (www.epistemonkos.org/): up to 2021/01/27
Searched: 27.1.21

(title:(((rectal* OR rectum* OR anal OR anus) AND (cancer* OR neoplas* OR oncolog* OR malignan* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR adenom* OR lesion*) AND (surger* OR surgical* OR resect* OR excision* OR operat* OR preoper* OR presurg* OR neoadjuvant))) OR abstract:(((rectal* OR rectum* OR anal OR anus) AND (cancer* OR neoplas* OR oncolog* OR malignan* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR adenom* OR lesion*) AND (surger* OR surgical* OR resect* OR excision* OR operat* OR preoper* OR presurg* OR neoadjuvant))))

Filtered: 2015-2021, Systematic Review, no Cochrane reviews
Epistemonikos retrieved 590 results

NHS Evidence (www.evidence.nhs.uk): up to 21/01/27
Searched 27.1.21

Search term – limited to guidance / systematic reviews, 01/01/2015-27/01/2021	Hits
("rectal cancer" or "rectal carcinoma" or "rectal carcinomas") and (surger* or surgical* or neoadjuvant or preoper* or presurg*)	215 (54 G, 161 SR)
Total	**215**

National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/guidance): up to 2021/01/21
Searched 26.1.21

Limited to (Published) Guidelines/ Nice Advice

Filter by title	Hits
Rectal Cancer	13
Rectum Cancer	0
Rectal Carcinoma	0
Rectum Carcinoma	0
Rectal neoplasms	0
Rectum neoplasms	0
Total	**13**
Total without duplicates	**13**

Guidelines International Network (GIN) Library (http://www.g-i-n.net): up to 2021/01/26
Searched: 26.1.21

Limited 2015-C

Search terms	Hits
rectal cancer	3
rectum cancer	1
Rectal carcinoma	0
Rectum carcinoma	0
Rectal neoplasm	3
Rectum neoplasm	1
Total	**8**
Total without duplicates	**4**

ECRI (www.guidelines.ecri.org): up to 28/01/21
Searched 28/01/21

Search terms	Hits
rectum cancer OR rectal cancer OR rectal carcinoma or rectum carcinoma	13
Total restricted to 2015 onwards	**13**

TRIP Database (https://www.tripdatabase.com/): up to 2021/01/26
Searched 26.1.21

Limited to Guidelines 2015 onwards

Keywords	Hits
(surger* or surgical* or resect* or excision* or operat* or neoadjuvant) ("rectal cancer" or "rectum cancer" or "rectal neoplasms" or "rectum neoplasms" or "rectal neoplasm" or "rectum neoplasm" or "rectal carcinoma" or "rectum carcinoma") from:2015	Aus & NZ = 6 Canada = 11 UK = 21 USA = 55 Other = 33
Total	**126**

SDM Searches

Embase (OVID): 1974 to 2021/01/27
Searched: 28.1.21
1 rectum cancer/ or rectum carcinoma/ (47941)
2 ((rectal$ or rectum$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (64234)
3 or/1-2 (76306)
4 exp surgery/ (4968669)
5 (surger$ or surgical$ or resect$ or excision$ or operat$ or preoper$ or presurg$ or neoadjuvant or TNT).ti,ab,ot. (3802742)
6 or/4-5 (6386893)
7 3 and 6 (52365)
8 *patient decision making/ or *shared decision making/ (4675)
9 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (54217)
10 sdm.ti,ab. (3649)
11 (decision$ adj2 aid$).ti,ab. (9116)
12 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (100700)
13 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (9433)
14 (person centred or person centered).ti,ab. (6978)
15 or/8-14 (177574)
16 7 and 15 (614)
17 limit 16 to yr="2016 -Current" (241)

MEDLINE(Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2021/01/26
Searched: 28.1.21
1 exp rectal neoplasm/ (48097)
2 ((rectal$ or rectum$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (43408)
3 or/1-2 (62969)

4 exp General Surgery/ (39268)
5 (surger$ or surgical$ or resect$ or excision$ or operat$ or preoper$ or presurg$ or neoadjuvant or TNT).ti,ab,ot. (2918112)
6 or/4-5 (2934528)
7 3 and 6 (32790)
8 exp Decision Making/ (207368)
9 exp decision support techniques/ (78554)
10 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (39904)
11 (decision$ adj2 aid$).ti,ab. (6273)
12 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (64506)
13 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (6908)
14 (person centred or person centered).ti,ab. (5802)
15 sdm.ti,ab. (2864)
16 or/8-15 (388701)
17 7 and 16 (560)
18 limit 17 to yr="2016 -Current" (187)