National Institute for Health and Care Excellence

Final

Colorectal cancer (update)

[C4] Deferral of surgery in people having neoadjuvant therapy for rectal cancer

NICE guideline NG151

Evidence reviews

January 2020

Final

Developed by the National Guideline Alliance part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Deferral of surgery in people having neoadjuvant therapy for rectal cancer

This evidence review supports recommendations 1.3.4 to 1.3.5.

Review question

Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

Introduction

People whose rectal cancer shows a complete clinical response to neoadjuvant therapy may choose to defer surgery, thereby avoiding the risk of surgical morbidity. However, despite having a complete clinical response some patients following such a watch and wait approach will experience locoregional recurrence or progression. This review question aimed to identify prognostic factors that predict recurrence and survival to better select people for watch and wait management.

Summary of protocol

Please see Table 1 for a summary of the population, prognostic factors, and outcomes (PPO) characteristics of this review.

Table 1: Summary of the protocol (PFO table)

Population	Adults with non-metastatic rectal cancer who have complete clinical response to neoadjuvant radiotherapy or chemoradiotherapy and are fit for, but who have not had, surgery.
Factors	• Patient characteristics ○ Age (life expectancy) • Disease characteristics ○ Radiological T stage ○ Radiological N stage ○ Radiological extra-mural vascular invasion ○ Tumour's distance from anal verge • Tumour pathology / biology (from pre-treatment biopsy) ○ Differentiation ○ Lymphovascular invasion (LVI) ○ *RAS* mutations ○ *BRAF* mutations ○ *MSI* • Carcinoembryonic antigen (CEA) levels ○ Pre-treatment ○ Post-chemoradiotherapy ○ Change from pre- to post-treatment • Tumour regression grade (TRG)
Outcomes	**Critical** • Locoregional progression or recurrence • Overall survival • Disease-free survival

	Important • Organ preservation rate

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CEA: carcinoembryonic antigen; LVI: lymphovascular invasion; MSI: microsatellite instability; RAS: rat sarcoma virus oncogene homolog; TRG: tumour regression grade.

For full details see the review protocol in appendix A

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

A systematic review of the clinical literature was conducted but no studies were identified which were applicable to this review question.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of clinical studies included in the evidence review

No studies were identified which were applicable to this review question (and so there are no evidence tables in appendix D). No meta-analysis was undertaken for this review (and so there are no forest plots in appendix E).

Quality assessment of clinical outcomes included in the evidence review

No studies were identified which were applicable to this review question.

Economic evidence

Included studies

One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic (Rao 2017; see appendix H and appendix I for summary and full evidence tables). The study considered the cost-effectiveness of watch and wait in comparison to radical surgery for patients with rectal cancer after a clinical complete response following chemoradiotherapy. The study considered three patient groups; 60 year old male cohort with no co-morbidities, 80 year old male cohort with no co-morbidities and 80 year old male cohort with significant co-morbidities.

The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs).

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Summary of studies included in the economic evidence review

The base case results of Rao 2017 suggest that watch and wait was found to be more effective and more costly than radical surgery in all modelled patient groups. The strategy was therefore dominant in all patient groups.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis. Results were found to be sensitive to relative recurrence rates after watch and wait (WW) and radical surgery as well as changes in the quality of life (QoL) reduction with radical surgery. It was also found that the model became sensitive to changes in perioperative mortality when the QoL benefit of WW was reduced. In probabilistic sensitivity analysis watch and wait was found to have a 74%, 85% and 90% probability of being cost-effective in the 60 year old male cohort, 80 year old male cohort with no co-morbidities and 80 year old male cohort with significant co-morbidities, respectively.

Despite being a UK study considering the NHS perspective, the study was considered to be only partially applicable. This is because it doesn't directly address the review question posed in the guideline (but it is partially addressed by the different subgroups considered in the analysis). Whilst the study meets most of the requirements of an adequate economic evaluation (see Developing NICE guidelines: appendix H), it was deemed to have some potentially serious limitations. Most notably, a key aspect of the analysis is the QoL gain with watch and wait and this is based on QoL values from another disease area (prostate cancer).

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

No clinical evidence was identified which was applicable to this review question.

Economic evidence statements

One relevant study was identified in the literature review of published cost effectiveness analyses on this topic (Rao 2017). This was a cost utility study, partially applicable to the decision problem with potentially serious methodological limitations, comparing radical surgery to a 'watch and wait' strategy involving outpatient imaging and monitoring in male patients who had had a complete response to neoadjuvant therapy and were suitable for surgery for rectal cancer. 'Watch and wait' was the dominant intervention in all subgroups leading to a reduction in both costs (ranging from £6,274 to £8,095) and an increase in QALYs (ranging from 0.56 to 0.72). Probabilistic sensitivity analysis estimated the probability of 'watch and wait' being cost effective when QALYs are valued at £20,000 each, is over 74% for all sub-groups.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Locoregional progression or recurrence was a critical outcome because it typically leads to further treatment with associated treatment related adverse effects. Overall survival and disease free survival were also critical outcomes because a watch and wait strategy (with deferred surgery) would only be safe if it did not impact survival. Organ preservation rate was an important outcome because organ preservation avoids the morbidity and functional consequences of major surgery.

The quality of the evidence

No evidence was identified which was applicable to this review question.

Benefits and harms

Surgery is the gold standard treatment for rectal cancer. However, some people whose rectal cancer shows a complete clinical response to neoadjuvant therapy wish to defer surgery and opt for an organ preserving 'watch and wait' strategy instead. The committee acknowledged that while the watch and wait strategy avoids harms due to surgery around one third will experience local regrowth of their tumour and need salvage surgery. Any local regrowth needs to be detected and treated to avoid disease progression, however this involves a surveillance protocol with repeated examinations which may be inconvenient for some patients.

No evidence was identified on the prognostic factors which could predict recurrence or survival, therefore, there is no evidence to help identify groups of patients for whom deferral of surgery would or would not be appropriate. The committee also recognised the lack of agreed definition of complete clinical or radiological response bringing further uncertainty to who might be candidates for deferral of surgery. For these reasons the committee could not recommend deferral of surgery.

The committee agreed that if a person wishes to defer surgery, they should be informed that there is no evidence to help define for whom deferral might be appropriate and that there is a risk of recurrence. If a person still chooses to defer surgery, deferral should only happen in the context of a clinical trial or a national registry where patients are closely monitored in order to detect and treat any local regrowth of their tumour. Patients should be encouraged to enter a clinical trial (for example on going trials OPERA or TRIGGER) and data collection via a national registry should be ensured. This would generate evidence in the future to help define groups that might benefit from deferral of surgery.

Cost effectiveness and resource use

One relevant study was identified in the literature review of published cost effectiveness analyses on this topic (Rao 2017). This was a cost utility study comparing radial surgery to a 'watch and wait' strategy involving outpatient imaging and monitoring in male patients who had had a complete response to neoadjuvant therapy and were suitable for surgery for rectal cancer. Three different patient groups were considered - 60 year olds with no comorbidities, 80 year olds with no comorbidities and 80 year olds with significant comorbidities. The model was a decision tree and markov model informed by previous estimates from the literature. All costs were taken from NHS reference costs and the analysis took a NHS & PSS perspective.

'Watch and wait' was the dominant intervention in all subgroups leading to a reduction in both costs (ranging from £6,274 to £8,095) and an increase in QALYs (ranging from 0.56 to 0.72). Deterministic sensitivity analysis was conducted in two ways. Alternative scenarios to

the base case were explored which involved applying National Comprehensive Cancer Network (NCCN) protocols for follow-up, correlated cost parameters or doubling all costs. Watch and wait remained dominant under all these alternate assumptions.

It was found that the results of the model were sensitive to relative recurrence rates after watch and wait and radical surgery as well as changes in the quality of life reduction with radical surgery. It was also found that the model became sensitive to changes in perioperative mortality when the quality of life benefit of 'watch and wait' was reduced. The model was not found to be sensitive to variations in baseline mortality and operative mortality or individual cost parameters. Probabilistic sensitivity analysis estimated the probability of 'watch and wait' being cost effective at a £20,000 per QALY threshold at over 74% for all sub-groups.

Despite being a recent UK cost effectiveness study it was deemed only partially applicable to the review questions as it did not directly address the review question posed in the guideline. The question was only partially addressed by the different subgroups considered. It was also deemed to have some potentially serious methodological limitations. Most notably, a key aspect of the analysis is the quality of life gain with 'watch and wait' and this is based on values from another disease area (prostate cancer).

The committee found the study to be of limited value in addressing the review question because it didn't consider the patient factors which were of most interest.

Other factors the committee took into account

The committee were aware of an international registry of patients with rectal cancer managed by a watch and wait strategy after complete clinical response to neoadjuvant therapy. Only a multicentre project like this is likely to collect sufficient patient numbers to answer the question of who is best suited to a watch and wait strategy. Also ongoing trials such as OPERA and TRIGGER may generate evidence in the future on who is most suitable for deferral of surgery. For this reason they chose not to make a research recommendation for a new trial.

References

Rao 2017

Rao C, Sun Myint A, Athanasiou T, et al. (2017) Avoiding Radical Surgery in Elderly Patients With Rectal Cancer Is Cost-Effective. Diseases of the Colon and Rectum 60(1): 30-42

Appendices

Appendix A – Review protocol

Review protocol for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

Table 2: Review protocol for deferral of surgery in people having neoadjuvant therapy for rectal cancer

Field (based on PRISMA-P)	Content
Review question	Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?
Type of review question	Prognostic/clinical prediction review
Objective of the review	To determine the predictors for people having neoadjuvant chemotherapy or chemoradiotherapy for rectal cancer who do not need surgery.
Eligibility criteria – population/disease/condition/issue/domain	Adults with non-metastatic rectal cancer who have complete clinical response to neoadjuvant radiotherapy or chemoradiotherapy and are fit for, but who have not had, surgery. Rectal cancer: defined as any tumour within 15 cm from anal verge excluding anal canal.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Included studies must have at least 5 of the following predictor variables in their models Predictors: • Patient characteristics ○ Age (life expectancy) • Disease characteristics ○ Radiological T stage ○ Radiological N stage ○ Radiological extra-mural vascular invasion ○ Tumour's distance from anal verge • Tumour pathology / biology (from pre-treatment biopsy) ○ Differentiation ○ Lymphovascular invasion (LVI) ○ *RAS* mutations ○ *BRAF* mutations ○ *MSI* • Carcinoembryonic antigen (CEA) levels ○ Pre-treatment ○ Post-chemoradiotherapy ○ Change from pre- to post-treatment • Tumour regression grade (TRG)
Confounding factors	Analysis should adjust for important confounding factors, such as: • Time interval between neoadjuvant therapy and response assessment • Active surveillance protocol

Field (based on PRISMA-P)	Content
Outcomes and prioritisation	Critical: • Locoregional progression/recurrence (minimally important difference [MID]: local progression risk > 5% for decision to have immediate surgery (time dependent)) • Overall survival (MID: statistical significance) • Disease-free survival (MID: statistical significance) Important: • Organ preservation rate (MID: statistical significance)
Eligibility criteria – study design	Include published full text papers: • Systematic reviews/meta-analyses of cohort studies • RCTs (post-hoc analysis from trials with long follow-up periods) • Prospective cohort studies • Retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: English-language All settings will be considered that consider medications and treatments available in the UK Studies published post 2000 Studies published post 2000 will be considered for this review question, as the guideline committee considered that significant advances have occurred in rectal cancer management since this time period and outcomes for patients with rectal cancer prior to 2000 are not the same as post 2000.
Proposed sensitivity/sub-group analysis, or meta-regression	In the case of high heterogeneity, the following factors will be considered: • Time interval between neoadjuvant therapy and response assessment • Active surveillance protocol
Selection process – duplicate screening/selection/analysis	Sifting, data extraction and appraisal of methodological quality will be performed by the systematic reviewer. Any disputes will be resolved in discussion with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched (to be confirmed by the Information Scientist): Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Dates: from 2000

Field (based on PRISMA-P)	Content
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format was used, see appendix D (clinical evidence tables) and H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Quality in prognostic studies (QUIPS) tool • ROBINS-I for non-randomised studies
Criteria for quantitative synthesis (where suitable)	Meta-analyses will be not be conducted for this prognostic review.
Methods for analysis – combining studies and exploring (in)consistency	The adjusted odds ratios and 95% confidence intervals will be plotted in RevMan, however pooled results will not be calculated. The forest plots will be used to visually see the studies alongside each other and to explore similarities and differences between studies.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CCTR: Cochrane Controlled Trials Register; CEA: carcinoembryonic antigen; CSDR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; HTA: Health Technology Assessment; LVI: lymphovascular invasion; MID: minimal important difference; MSI: microsatellite instability; NGA: National Guidelines Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols; PROSPERO: International prospective register of systematic reviews; QUIPS: Quality in prognostic studies; RAS: rat sarcoma virus oncogene homolog; RCT: randomised controlled trial; ROBINS-I: risk of bias in non-randomised studies of interventions; ROBIS: risk of bias in systematic reviews; TNM: cancer classification system, standing for tumour, nodal and metastasis stages; QUIPS: quality in prognosis studies

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: Which people having 3 neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need 4 surgery?

5 Database: Embase/Medline

6 Last searched on: 12/02/2019

#	Search
1	exp Rectal Neoplasms/ use prmz
2	*rectum cancer/ or *rectum tumor/
3	2 use oemezd
4	exp Adenocarcinoma/
5	(T1 or T2 or N0 or M0).ti,ab.
6	1 or 3
7	4 or 5
8	6 and 7
9	((rectal or rectum) adj3 (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)).ti,ab.
10	early rect* cancer.ti,ab.
11	6 or 8 or 9 or 10
12	exp radiotherapy/ or exp radiation oncology/ or exp external beam radiotherapy/ or exp Brachytherapy/ or exp preoperative care/ or exp neoadjuvant therapy/ or exp multimodality cancer therapy/ or exp chemotherapy/ or exp antineoplastic agent/ or exp drug therapy/ or exp chemoradiotherapy/ or exp fluorouracil/ or exp folinic acid/ or exp capecitabine/ or exp oxaliplatin/ or exp bevacizumab/ or exp methotrexate/ or exp radiation dose fractionation/ or exp tumor recurrence/ or exp radiotherapy dosage/
13	12 use oemezd
14	exp Radiotherapy/ or exp Radiation Oncology/ or exp Radiotherapy, Computer-Assisted/ or exp Brachytherapy/ or exp Preoperative Care/ or exp Neoadjuvant Therapy/ or exp Combined Modality Therapy/ or exp Chemoradiotherapy/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Drug Therapy/ or exp Antineoplastic Agents/ or exp Fluorouracil/ or exp Leucovorin/ or exp Capecitabine/ or exp Bevacizumab/ or exp Methotrexate/ or exp Dose Fractionation/ or exp radiotherapy dosage/
15	14 use prmz
16	((radiotherap* or chemoradio* or radiation or brachytherapy* or chemotherapy*) adj (pre?op* or preop* or periop* or neoadjuvant)).ti,ab.
17	(5-fluorouracil or 5-FU or leucovorin or folinic acid or capecitabine or oxaliplatin or bevacizumab or methotrexate or dose* or fraction* or recurren*).ti,ab.
18	13 or 15 or 16 or 17
19	exp Organ Preservation/ or Organ Sparing Treatments/ or exp Treatment Outcome/ or exp Disease-Free Survival/ or exp Neoplasm Recurrence, Local/ or exp Neoplasm, Residual/ or exp Lymph Nodes/ or exp Risk Factors/ or exp Prognosis/ or exp Observation/ or exp Watchful Waiting/ or exp Time Factors/ or exp Comorbidity/ or exp Age Factors/ or exp Health Status/ or exp Health Status Indicators/ or exp Morbidity/ or exp Physical Fitness/
20	19 use prmz
21	exp organ preservation/ or exp conservative treatment/ or exp treatment outcome/ or exp disease free survival/ or exp tumor recurrence/ or exp minimal residual disease/ or lymph node/ or exp lymph node/ or exp risk factor/ or exp prognosis/ or exp observation/ or exp watchful waiting/ or exp time factor/ or exp adjuvant therapy/ or exp cancer control/ or exp comorbidity/ or exp health status indicator/ or exp morbidity/ or age/ or exp performance/ or fitness/ or (exp patient/ and exp health status/)
22	21 use oemezd
23	(prognos* or preservation or preserve* or sparing or complete response* or predict* or watch* or wait* or observ* or risk* or regrowth or recurren* or adjuvant or downstag* or downsize* or local control or residual or morbid* or poor perform* or delay* or unfit or fit or (lymph node adj (count or status)) or histolog* or outcome or ((avoid* or suit*) adj3 surger*)).ti,ab.
24	20 or 22 or 23
25	11 and 18 and 24
26	limit 25 to english language
27	limit 26 to yr="2000 -Current"
28	(conference abstract or letter).pt. or letter/ or editorial.pt. or note.pt. or case report/ or case study/ use oemezd
29	Letter/ or editorial/ or news/ or historical article/ or anecdotes as topic/ or comment/ or case report/ use prmz
30	(letter or comment* or abstracts).ti.
31	or/28-30
32	randomized controlled trial/ use prmz
33	randomized controlled trial/ use oemezd
34	random*.ti,ab.
35	or/32-34
36	31 not 35
37	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ use prmz

#	Search
38	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ use oemezd
39	(rat or rats or mouse or mice).ti.
40	36 or 37 or 38 or 39
41	27 not 40

1 **Database: Cochrane Library**

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Rectal Neoplasms] explode all trees
2	MeSH descriptor: [Adenocarcinoma] explode all trees
3	T1 or T2 or N0 or M0
4	#2 or #3
5	#1 and #4
6	(rectal or rectum) near (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)
7	early rect* cancer
8	#1 or #5 or #6 or #7
9	MeSH descriptor: [Radiotherapy] explode all trees
10	MeSH descriptor: [Radiation Oncology] explode all trees
11	MeSH descriptor: [Radiotherapy, Computer-Assisted] explode all trees
12	MeSH descriptor: [Brachytherapy] explode all trees
13	MeSH descriptor: [Preoperative Care] explode all trees
14	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
15	MeSH descriptor: [Combined Modality Therapy] explode all trees
16	MeSH descriptor: [Chemoradiotherapy] explode all trees
17	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
18	MeSH descriptor: [Drug Therapy] explode all trees
19	MeSH descriptor: [Antineoplastic Agents] explode all trees
20	MeSH descriptor: [Fluorouracil] explode all trees
21	MeSH descriptor: [Capecitabine] explode all trees
22	MeSH descriptor: [Bevacizumab] explode all trees
23	MeSH descriptor: [Methotrexate] explode all trees
24	MeSH descriptor: [Dose Fractionation] explode all trees
25	(radiotherap* or chemoradio* or radiation or brachytherapy* or chemotherapy*) near (pre?op* or preop* or periop* or neoadjuvant)
26	5-fluorouracil or 5-FU or leucovorin or folinic acid or capecitabine or oxaliplatin or bevacizumab or methotrexate or dose* or fraction* or recurren*
27	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
28	MeSH descriptor: [Organ Preservation] explode all trees
29	MeSH descriptor: [Organ Sparing Treatments] explode all trees
30	MeSH descriptor: [Treatment Outcome] explode all trees
31	MeSH descriptor: [Disease-Free Survival] explode all trees
32	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
33	MeSH descriptor: [Neoplasm, Residual] explode all trees
34	MeSH descriptor: [Lymph Nodes] explode all trees
35	MeSH descriptor: [Risk Factors] explode all trees
36	MeSH descriptor: [Prognosis] explode all trees
37	MeSH descriptor: [Observation] explode all trees
38	MeSH descriptor: [Watchful Waiting] explode all trees
39	MeSH descriptor: [Time Factors] explode all trees
40	prognos* or preservation or preserve* or sparing or complete response* or predict* or watch* or wait* or observ* or risk* or regrowth or recurren* or adjuvant or downstag* or downsize* or local control or residual or histolog* or outcome
41	lymph node near (count or status)
42	(avoid* or suit*) near surger*
43	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
44	#8 and #27 and #43 Publication Year from 2000 to 2018

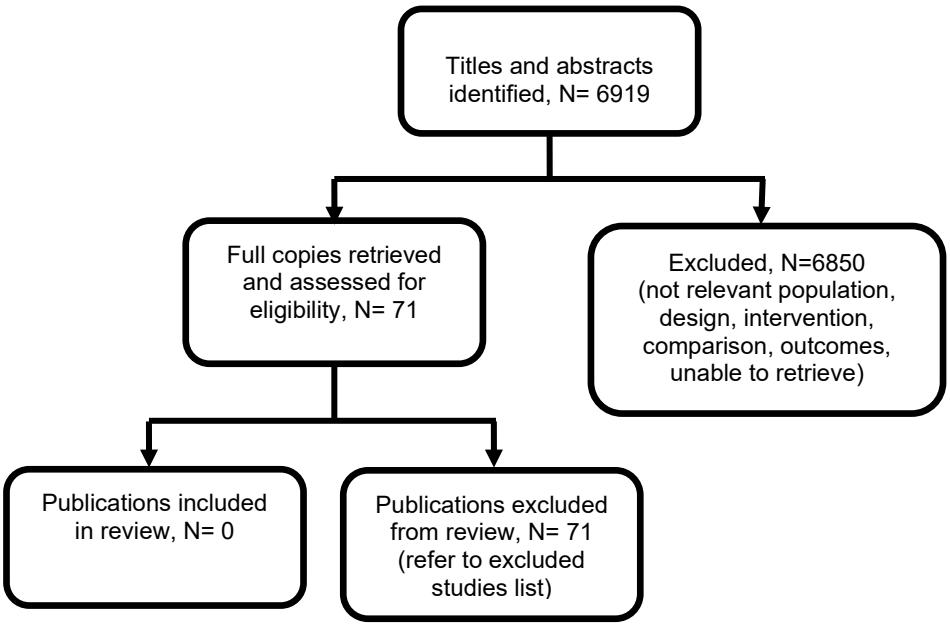
3

4

Appendix C – Clinical evidence study selection

Clinical study selection for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

No clinical evidence was identified which was applicable to this review question.

Appendix E – Forest plots

Forest plots for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

No clinical evidence was identified which was applicable to this review question.

Appendix F – GRADE tables

GRADE tables for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

No clinical evidence was identified which was applicable to this review question.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

1 Appendix H – Economic evidence tables

2 Economic evidence tables for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal 3 cancer do not need surgery?

4 **Table 3: Economic evidence tables for deferral of surgery in people having neoadjuvant therapy for rectal cancer**

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Rao 2017 **Country:** United Kingdom **Type of economic analysis:** Cost Utility Analysis (CUA) **Source of funding:** Author was supported by the National Institutes of Health Research Collaboration for Leadership in Applied Health	**Interventions in detail:** Radical surgery It was assumed that patients would be followed-up after surgery in accordance with national guidelines, which recommend a minimum of 2 CTs of the chest, abdomen, and pelvis in the first 3 years. In addition, a surveillance colonoscopy is offered at 1 year. Watch and wait Surveillance strategy for watch and wait is not stated explicitly but from an accompanying diagram it can be seen	**Population characteristics:** All patients enter the model with a clinical complete response following neoadjuvant chemoradiotherapy. The study considered three hypothetical patient groups: • 60 year old male cohort with no co-morbidities • 80 year old male cohort with no co-morbidities • 80 year old male cohort with significant co-morbidities. **Modelling approach:** Decision tree and Markov model **Source of base-line and effectiveness data:** Estimates of postoperative mortality in the first 90 days were obtained from the Hospital Episodes Statistics	**60 year old male cohort with no co-morbidities** **Incremental costs with watch and wait:** -£8,095 **Incremental QALYs with watch and wait:** 0.63 QALYs **ICER:** Dominant **80 year old male cohort with no co-morbidities** **Incremental costs with watch and wait:** -£6,274 **Incremental QALYs with watch and wait:** 0.56 QALYs **ICER:** Dominant **80 year old male cohort with significant co-morbidities** **Incremental costs with watch and wait:**	**Perspective:** Third-party payer perspective – UK NHS. **Currency:** US dollars ($) using an exchange rate of $1.4:1 UK pound sterling (£). UK pound sterling values are also presented and these have been reported here. **Cost year:** Not reported but most costs are based on NHS Reference costs 2014/15 **Time horizon:** Not reported but it appears that a lifetime

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Research and Care North West Coast.	that it involves outpatient appointments, imaging with CT scans and MRIs, flexible sigmoidoscopy, colonoscopy and CEA tests.	database. Baseline mortality estimates were sourced from UK national life tables (ONS). Estimates of other clinical parameters were sourced from published literature and were in-line with a previously published decision analysis. **Source of cost data:** Costs were all sourced from NHS reference costs 2014-15 using the appropriate code. **Source of QoL data:** QoL estimates for baseline QoL (i.e. complete response following chemoradiotherapy) were based on a value from the prostate cancer literature (authors state that no suitable rectal cancer data was available). QoL values for other health states were based on data from a Dutch Total Mesorectal Excision study (Van Den Brink 2004) and a previous cost-utility analysis on the management of recurrent rectal cancer (Miller 2000).	-£7,290 **Incremental QALYs with watch and wait:** 0.72 QALYs **ICER:** Dominant **Deterministic sensitivity analysis:** Deterministic sensitivity analysis was conducted in two ways. Alternative scenarios to the base case were explored which involved applying National Comprehensive Cancer Network (NCCN) protocols for follow-up, correlated cost parameters or doubling all costs. The conclusion of the analysis was found to be the same as in the base case (i.e. watch and wait was found to be dominant). Deterministic sensitivity analysis was also performed using bivariate sensitivity analysis. It was found that the results of the model were sensitive to relative recurrence rates after watch and wait and radical surgery as well as changes in the QoL reduction with radical surgery. It was also found that the model became sensitive to changes in perioperative mortality when the QoL benefit of WW was reduced The model was not found to be sensitive to variations in baseline mortality and operative mortality or individual cost parameters.	perspective has been adopted. **Discounting:** 3.5% per year **Applicability:** Despite being a UK study considering the NHS perspective, the study was considered to be only *partially applicable*. This is because it doesn't directly address the review question posed in the guideline (but it is partially addressed by the different subgroups considered in the analysis). **Limitations:** Whilst the study meets most of the requirements of an adequate economic evaluation (see Developing NICE guidelines: appendix H), it was deemed to have some potentially serious limitations. Most notably, a key aspect of

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			Probabilistic sensitivity analysis: Probabilistic sensitivity analysis was conducted. At the NICE threshold of £20,000 per QALY, watch and wait was found to have a: • 74% probability of being cost-effective in the 60 year old male cohort with no co-morbidities •85% probability of being cost-effective in the 80 year old male cohort with no co-morbidities • 90% probability of being cost-effective in the 80 year old male cohort with significant co-morbidities Probabilistic sensitivity analysis was also performed for the alternative scenarios considered in the deterministic sensitivity analysis. They remained favourable for watch and wait in all scenarios.	the analysis is the QoL gain with watch and wait and this is based on QoL values from another disease area (prostate cancer). It is also unclear whether all clinical parameters in the model were sourced using a systematic review evidence. The time horizon considered in the analysis is also unclear. **Other comments:**

CEA: carcinoembryonic antigen; CT: computed tomography; CUA: cost utility analysis; ICER: incremental cost effectiveness ratio; MRI: magnetic resonance imaging; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ONS: Office for National Statistics; QALY: quality adjusted life year; QoL: quality of life; WW: watch and wait

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

Table 4: Economic evidence profiles for people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Rao 2017	Patients with a clinical complete response following neoadjuvant chemoradiotherapy	60 year old male cohort with no co-morbidities						Deterministic sensitivity analysis was conducted. The results were found to be sensitive to relative recurrence rates after watch and wait and radical surgery as well as changes in the QoL reduction with radical surgery. It was also found that the model became sensitive to changes in perioperative mortality when the QoL benefit of WW was reduced The study included a probabilistic sensitivity analysis. At the NICE threshold of £20,000 per QALY, watch and wait was found to have a: • 74% probability of being cost-effective in the 60 year old male cohort with no co-morbidities	Despite being a UK study considering the NHS perspective, the study was considered to be only partially applicable. This is because it doesn't directly address the review question posed in the guideline (but it is partially addressed by the different subgroups considered in the analysis). The study was deemed to have some potentially serious limitations. It is unclear whether model parameters were sourced using a systematic review of clinical evidence. The time horizon considered in the
		Radical surgery	Not reported	Not reported	Reference				
		Watch and wait	Not reported	Not reported	-£8,095	0.63 QALYs	Dominant		
		80 year old male cohort with no co-morbidities							
		Radical surgery	Not reported	Not reported	Reference				
		Watch and wait	Not reported	Not reported	-£6,274	0.56 QALYs	Dominant		
		80 year old male cohort with significant co-morbidities							
		Radical surgery	Not reported	Not reported	Reference				
		Watch and wait	Not reported	Not reported	-£7,290	0.72 QALYs	Dominant		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
								•85% probability of being cost-effective in the 80 year old male cohort with no co-morbidities • 90% probability of being cost-effective in the 80 year old male cohort with significant co-morbidities	analysis is also unclear.
	Comments: Results in study are primarily reported in US dollars (using an exchange rate of $1.4:£1) but UK costs are also reported in most instances and these have been presented here.								

ICER: incremental cost-effectiveness ratio; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; QALY: quality adjusted life year; QoL: quality of life; WW: watch and wait

Appendix J – Economic analysis

Economic evidence analysis for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: Which people having neoadjuvant 3 radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

4 **Table 5: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Abrams, M. J., Koffer, P. P., Leonard, K. L., The emerging non-operative management of non-metastatic rectal cancer: A population analysis, Anticancer Research, 36, 1699-1702, 2016	Patients not selected for complete clinical response
Alongi, F., Mazzola, R., Watch-and-wait versus surgical resection for patients with rectal cancer, The Lancet Oncology, 17, e133-e134, 2016	Letter in response to Renehan (2015)
Appelt, A. L., Ploen, J., Harling, H., Jensen, F. S., Jensen, L. H., Jorgensen, J. C. R., Lindebjerg, J., Rafaelsen, S. R., Jakobsen, A., High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study, The Lancet Oncology, 16, 919-927, 2015	No analysis of prognostic factors
Araujo, R. O. C., Valadao, M., Borges, D., Linhares, E., De Jesus, J. P., Ferreira, C. G., Victorino, A. P., Vieira, F. M., Albagli, R., Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study, European Journal of Surgical Oncology, 41, 1456-1463, 2015	No multivariate prognostic analysis. Univariate data for: distance from anal verge.
Bannura, G., Outcome and salvage surgery following "watch and wait" for rectal cancer after neoadjuvant therapy: A systematic review, Revista Chilena de Cirugia, 352, 2017	Non English language
Beets, G. L., Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation, British Journal of Surgery, 99, 910, 2012	Commentary on systematic review (Glynne-Jones. 2012)
Beets, G. L., What are We Going to Do with Complete Responses After Chemoradiation of Rectal Cancer?, Annals of Surgical Oncology, 23, 1801-1802, 2016	Expert review
Beets, G. L., Figueiredo, N. L., Habr-Gama, A., Van De Velde, C. J. H., A new paradigm for rectal cancer: Organ preservation Introducing the International Watch & Wait Database (IWWD), European Journal of Surgical Oncology, 41, 1562-1564, 2015	Describes watch-and-watch international database.
Benezery, K., Chamorey, E., Francois, E., Doyen, J., Gourgou-Bourgade, S., Gerard, J. P., Clinical complete response after neoadjuvant chemoradiotherapy (nCRT) of rectal cancer: A key end point to increase conservative treatment - Findings from the ACCORD12 randomized trial, European Journal of Cancer, 49, S501-S502, 2013	Conference abstract
Bhangu, A., Kiran, R. P., Audisio, R., Tekkis, P., Survival outcome of operated and non-operated elderly patients with rectal cancer: A Surveillance, Epidemiology, and End Results analysis, European Journal of Surgical Oncology, 40, 1510-1516, 2014	Complete clinical response not an inclusion criteria
Bhatti, A. B. H., Zaheer, S., Shafique, K., Prognostic role of acellular mucin pools in patients with rectal cancer after pathological complete response to preoperative chemoradiation: Systematic review and meta-analysis, Journal of the College of Physicians and Surgeons Pakistan, 27, 714-718, 2017	Patients had surgery
Brooker, R., McKay, M., Crabtree, A., Wong, H., Sripadam, R., Organ sparing radiotherapy in rectal cancer: Definitive chemoradiation is a safe and valid option, Annals of Oncology, 26, iv96, 2015	Conference abstract

Study	Reason for exclusion
Caderillo-Ruiz, G., Diaz, C., Lopez-Basave, H. N., Herrera, M. T., Ruiz Garcia, E., Melchor, J., Trejo, G., Aguilar, J. L., Gomez, A. H., Meneses-Garcia, A., Clinical outcome in patients who did not accept complementary surgery after neoadjuvant chemoradiotherapy (QT-RT) in locally advanced rectal cancer (LARC), Journal of Clinical Oncology. Conference, 34, 2016	Conference abstract
Cotti, G., Nahas, C., Marques, C., Imperiale, A., Ribeiro Jr, U., Nahas, S., Cecconello, I., Hoff, P., Outcomes of nonsurgical treatment in patients with clinical complete response after neoadjuvant therapy for rectal cancer, Diseases of the Colon and Rectum, 59 (5), e262, 2016	Conference abstract
Dattani, M., Heald, R. J., Goussous, G., Broadhurst, J., Sao Juliao, G. P., Habr-Gama, A., Perez, R. O., Moran, B. J., Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis, Annals of Surgery, 268, 955-967, 2018	Does not report prognostic analysis
Dickson-Lowe, R. A., Hanek, P., Kalaskar, S., Taylor, J., Non-operative management of low rectal cancer with complete response to standard neoadjuvant chemoradiotherapy, Gut, 1), A554-A555, 2015	Conference abstract
Dossa, F., Chesney, T. R., Acuna, S. A., Baxter, N. N., A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis, The Lancet Gastroenterology and Hepatology, 2, 501-513, 2017	Systematic review, does not report prognostic factor analysis.
Glynne-Jones, R., Hughes, R., Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation, British Journal of Surgery, 99, 897-909, 2012	Systematic review, does not report prognostic factor analysis.
Glynne-Jones, R., Wallace, M., Livingstone, J. I. L., Meyrick-Thomas, J., Complete clinical response after preoperative chemoradiation in rectal cancer: Is a "wait and see" policy justified?, Diseases of the Colon and Rectum, 51, 10-19, 2008	Earlier version of Glynne-Jones (2012) systematic review
Gossedge, G., Montazeri, A., Nandhra, A., Wong, H., Artioukh, D., Zeiderman, M., Chipang, A., Myint, A., Complete clinical response to chemoradiotherapy for rectal cancer. Is it safe to 'watch and wait'?, Colorectal Disease, 2), 20, 2012	Conference abstract
Habr-Gama, A., Gama-Rodrigues, J., Sao Juliao, G. P., Proscurshim, I., Sabbagh, C., Lynn, P. B., Perez, R. O., Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: Impact of salvage therapy on local disease control, International Journal of Radiation Oncology Biology Physics, 88, 822-828, 2014	No multivariate prognostic analysis. Univariate data for: T stage, N stage.
Habr-Gama, A., Perez, R. O., Nadalin, W., Sabbaga, J., Ribeiro, U., Jr., Silva e Sousa, A. H., Jr., Campos, F. G., Kiss, D. R., Gama-Rodrigues, J., Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results, Annals of Surgery, 240, 711-7; discussion 717-8, 2004	No prognostic factor analysis
Habr-Gama, A., Perez, R. O., Proscurshim, I., Campos, F. G., Nadalin, W., Kiss, D., Gama-Rodrigues, J., Patterns of Failure and Survival for Nonoperative Treatment of Stage c0 Distal Rectal Cancer Following Neoadjuvant Chemoradiation Therapy, Journal of Gastrointestinal Surgery, 10, 1319-1329, 2006	No multivariate prognostic analysis. Univariate data for: T stage, N stage.
Habr-Gama, A., Sabbaga, J., Gama-Rodrigues, J., Sao Juliao, G. P., Proscurshim, I., Bailao Aguilar, P., Nadalin, W., Perez, R. O., Watch and wait approach following extended neoadjuvant chemoradiation	No multivariate prognostic analysis. Univariate data for: T stage, N stage.

Study	Reason for exclusion
for distal rectal cancer: are we getting closer to anal cancer management?, Diseases of the Colon & RectumDis Colon Rectum, 56, 1109-17, 2013	
Habr-Gama, A., Sao Juliao, G. P., Perez, R. O., Nonoperative management of rectal cancer: Identifying the ideal patients, Hematology/Oncology Clinics of North America, 29, 135-151, 2015	Expert review
Heijnen, L. A., Maas, M., Martens, M. H., Lambregts, D. M. J., Van Drie, E., Stassen, L. P. S., Breukink, S. O., Leijtens, J. W. A., Beets-Tan, R. G. H., Beets, G. L., Endoscopy-based follow-up of clinical complete responders after chemoradiation for rectal cancer during a non-operative 'wait-and-see' policy, European Journal of Cancer, 2), S485, 2013	Conference abstract
Hupkens, B., Martens, M., Kusters, M., Boelens, P., Meershoek-Klein Kranenbarg, E., Van Gestel, M., Ribeiro, R., Peeters, K., Perez, R., Figueiredo, N., Habr-Gama, A., Van De Velde, C., Beets, G., International watch and wait database: An international database of organ-preservation in rectal cancer, Colorectal Disease, 2), 68, 2015	Conference abstract
Iseas IS, Carballido M, Coraglio M, et al. , Moving forward and beyond the standard through a non-operative management in rectal cancer? Our watch and wait approach experience in CoRecto., Proc Am Soc Clin Oncol, 33, 2015	Conference abstract
Jafari, M. D., Weiser, M. R., Personalizing Therapy for Locally Advanced Rectal Cancer, Current Colorectal Cancer Reports, 13, 119-125, 2017	Expert review
Kessler, H., Matzel, K., Merkel, S., Fietkau, R., Hohenberger, W., Results of a "watch and wait" strategy in complete remission of rectal carcinoma after chemoradiotherapy, Diseases of the Colon and Rectum, 56 (4), e205, 2013	Conference abstract
Kim, H. J., Song, J. H., Ahn, H. S., Choi, B. H., Jeong, H., Choi, H. S., Lee, Y. H., Kang, K. M., Jeong, B. K., Wait and see approach for rectal cancer with a clinically complete response after neoadjuvant concurrent chemoradiotherapy, International Journal of Colorectal Disease, 32, 723-727, 2017	Systematic review, does not report prognostic factor analysis.
Kong, J. C., Guerra, G. R., Warrier, S. K., Ramsay, R. G., Heriot, A. G., Outcome and Salvage Surgery Following "Watch and Wait" for Rectal Cancer after Neoadjuvant Therapy: A Systematic Review, Diseases of the Colon and Rectum, 60, 335-345, 2017	Systematic review, does not report prognostic factor analysis.
Kusters, M., Slater, A., Betts, M., Hompes, R., Guy, R. J., Jones, O. M., George, B. D., Lindsey, I., Mortensen, N. J., James, D. R., Cunningham, C., The treatment of all MRI-defined low rectal cancers in a single expert centre over a 5-year period: is there room for improvement?, Colorectal Disease, 18, O397-O404, 2016	Outcomes not reported for watch
Lai, C. L., Lai, M. J., Wu, C. C., Jao, S. W., Hsiao, C. W., Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait", International Journal of Colorectal Disease, 31, 413-419, 2016	Does not report prognostic analysis.
Lambregts, D. M., Maas, M., Van Der Sande, M., Hupkens, B., Martens, M., Bakers, F., Beets-Tan, R. G. H., Breukink, S. O., Beets, G. L., Improving the selection of complete responders for watchful waiting after chemoradiotherapy for rectal cancer: What can we learn from the 'missed' pathologic complete responders after surgery?, United European Gastroenterology Journal, 5 (5 Supplement 1), A324, 2017	Abstract only.
Latif, M, Day, N, Montazeri, A, Wait & see policy following complete clinical response to chemoradiotherapy in rectal cancer, single centre experience, Annals of oncology. Conference: 16th world congress on	Conference abstract

Study	Reason for exclusion
gastrointestinal cancer, ESMO 2014. Spain. Conference start: 20140625. Conference end: 20140628, 25, ii102-ii103, 2014	
Li, J., Li, L., Yang, L., Yuan, J., Lv, B., Yao, Y., Xing, S., Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: A systematic review and meta-analysis, Oncotarget, 7, 44857-44870, 2016	Systematic review, No prognostic analysis reported.
Li, J., Liu, H., Yin, J., Liu, S., Hu, J., Du, F., Yuan, J., Lv, B., Fan, J., Leng, S., Zhang, X., Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: A cohort study, Oncotarget, 6, 42354-42361, 2015	No prognostic analysis reported.
Maas, M, Beets-Tan, Rgh, Lambregts, Dmj, Lammering, G, Nelemans, Pj, Engelen, Sme, Dam, Rm, Jansen, Rlh, Sosef, M, Leijtens, Jwa, Hulsewe, Kwe, Buijsen, J, Beets, Gl, Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer, Journal of Clinical Oncology, 29, 4633-4640, 2011	No multivariate prognostic analysis. Univariate data for: T stage, N stage, distance from anal verge.
Martens, M. H., Maas, M., Heijnen, L. A., Lambregts, D. M. J., Leijtens, J. W. A., Stassen, L. P. S., Breukink, S. O., Hoff, C., Belgers, E. J., Melenhorst, J., Jansen, R., Buijsen, J., Hoofwijk, T. G. M., Beets-Tan, R. G. H., Beets, G. L., Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer, Journal of the National Cancer InstituteJ Natl Cancer Inst, 108 (12) (no pagination), 2016	No multivariate prognostic analysis. Univariate data for: T stage, N stage.
Mendoza, A. G., Morales, R. D., Russo, L., The first Venezuelan experience in nonoperative management of rectal cancer with complete clinical response following neoadjuvant therapy, Revista Venezolana de Oncologia, 29, 65-75, 2017	Not English language
Myint, As, Smith, F, Whitmarsh, K, Wong, H, Pritchard, M, Non surgical treatment of operable rectal cancer: reducing harm from the standard of care in elderly patients, European journal of surgical oncology. Conference: joint BASO-ACS annual scientific conference and NCRI cancer conference 2016. United kingdom. Conference start: 20161106. Conference end: 20161109, 42, S228-s229, 2016	Conference abstract
Nahas, C. S., Nahas, S. C., Marques, C. F., Ribeiro Jr, U., Bustamante- Lopez, L. A., Cecconello, I., Randomized controlled trial for complete clinical response in patients with locally advanced rectal cancer after neoadjuvant chemoradiotherapy: Observation versus surgical resection, European Journal of Surgical Oncology, 41, S148, 2015	Conference abstract
Nahas, S., Nahas, C., Ribeiro Jr, U., Sparapan Marques, C., Cotti, G. C., Imperiale, A., Ortega, C., Azambuja, R., Chen, A., Hoff, P., Cecconello, I., Observation versus surgical resection in patients with rectal cancer who achieved complete clinical response after neoadjuvant chemoradiotherapy: Preliminary results of a randomized trial (NCT02052921), Diseases of the Colon and Rectum, 58 (5), e103-e104, 2015	Conference abstract
Nahas, Sc, Rizkallah, Nahas Cs, Sparapan, Marques Cf, Ribeiro, U, Cotti, Gc, Imperiale, Ar, Capareli, Fc, Chih, Chen At, Hoff, Pm, Cecconello, I, Pathologic Complete Response in Rectal Cancer: can We Detect It? Lessons Learned From a Proposed Randomized Trial of Watch-and-Wait Treatment of Rectal Cancer, Diseases of the Colon and Rectum, 59, 255-263, 2016	N=4, no recurrence events.
Narang, S., Alam, N., Smart, N., Daniels, I., Non-operative management of Rectal Cancer: Too much hype?, Colorectal Disease, 2), 15, 2015	Conference abstract

Study	Reason for exclusion
Neuman, H. B., Elkin, E. B., Guillem, J. G., Paty, P. B., Weiser, M. R., Wong, W. D., Temple, L. K., Treatment for patients with rectal cancer and a clinical complete response to neoadjuvant therapy: A decision analysis, Diseases of the Colon and Rectum, 52, 863-871, 2009	Decision model (not a primary study) - relapse rates during observation alone based on expert opinion.
Perez, R. O., Habr-Gama, A., Gama-Rodrigues, J., Proscurshim, I., Juliao, G. P. S., Lynn, P., Ono, C. R., Campos, F. G., Silva, E. Sousa Jr A. H., Imperiale, A. R., Nahas, S. C., Buchpiguel, C. A., Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: Long-term results of a prospective trial (National Clinical Trial 00254683), Cancer, 118, 3501-3511, 2012	Combines surgically and non-surgically treated patients
Rao, C., Sun Myint, A., Athanasiou, T., Faiz, O., Martin, A. P., Collins, B., Smith, F. M., Avoiding Radical Surgery in Elderly Patients With Rectal Cancer Is Cost-Effective, Diseases of the Colon & RectumDis Colon Rectum, 60, 30-42, 2017	Cost effectiveness study
Renehan, A. G., Malcomson, L., Emsley, R., Watch-and-wait approach for rectal cancer: concepts of a subject-specific method, The Lancet Gastroenterology and Hepatology, 2, 627, 2017	Letter in response to Dossa (2017) meta-analysis.
Renehan, A. G., Malcomson, L., Emsley, R., Gollins, S., Maw, A., Myint, A. S., Rooney, P. S., Susnerwala, S., Blower, A., Saunders, M. P., Wilson, M. S., Scott, N., O'Dwyer, S. T., Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): A propensity-score matched cohort analysis, The Lancet Oncology, 17, 174-183, 2016	No multivariate prognostic analysis for the watch and wait group
Renehan, A. G., Malcomson, L., Emsley, R., Scott, N., O'Dwyer, S. T., Watch-and-wait versus surgical resection for patients with rectal cancer - Authors' reply, The Lancet Oncology, 17, e134-e135, 2016	Authors reply to a letter in response to Rehenan (2015)
Sammour, T., Price, B. A., Krause, K. J., Chang, G. J., Nonoperative Management or 'Watch and Wait' for Rectal Cancer with Complete Clinical Response After Neoadjuvant Chemoradiotherapy: A Critical Appraisal, Annals of Surgical Oncology, 24, 1904-1915, 2017	Systematic review, prognostic analysis not reported
Sanchez Loria, F., Iseas, S., O'Connor, J. M., Pairola, A., Chacon, M., Mendez, G., Coraglio, M., Mariani, J., Dieguez, A., Roca, E., Huertas, E., Non-surgical management of rectal cancer. Series of 68 cases, long follow up in two leading centres in Argentina, Digestive and Liver Disease, 48, 1372-1377, 2016	No multivariate prognostic analysis. Univariate data for: T stage, N stage, CEA.
Schumacher, A., Rao, A., Loh, B. D., Dudukgian, H., Aboulian, A., McLemore, E. C., Attaluri, V., Rectal cancer: Nonoperative watch and wait vs standard of care surgical total mesorectal excision after complete clinical response to chemoradiation, a prospective cohort study, Journal of the American College of Surgeons, 225 (4 Supplement 1), S45, 2017	Conference abstract
Seshadri, R. A., Kondaveeti, S. S., Jayanand, S. B., John, A., Rajendranath, R., Arumugam, V., Ellusamy, H. R., Sagar, T. G., Complete clinical response to neoadjuvant chemoradiation in rectal cancers: Can surgery be avoided?, Hepato-Gastroenterology, 60, 410-414, 2013	Does not report analysis adjusted for confounders
Smith, F. M., Al-Amin, A., Wright, A., Berry, J., Nicoll, J. J., Sun Myint, A., Contact radiotherapy boost in association with 'watch and wait' for rectal cancer: initial experience and outcomes from a shared programme between a district general hospital network and a regional oncology centre, Colorectal Disease, 18, 861-870, 2016	Entry criteria were not complete clinical response (some chose nonoperative management for other reasons).
Smith, F. M., Rao, C., Perez, R. O., Bujko, K., Athanasiou, T., Habr-Gama, A., Faiz, O., Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical	Decision model (not primary study) - relapse rates during observation

Study	Reason for exclusion
response after neoadjuvant therapy: Results of a decision-analytic model, Diseases of the Colon and Rectum, 58, 159-171, 2015	alone based on expert opinion.
Smith, F., Rao, C., Perez, R., Bujko, K., Athanasiou, T., Habr-Gama, A., Faiz, O., Avoiding radical surgery improves survival in elderly patients with rectal cancer demonstrating complete clinical response following neoadjuvant therapy: Results of a decision analytical model, Colorectal Disease, 2), 63, 2014	Conference abstract
Smith, J. D., Ruby, J. A., Goodman, K. A., Saltz, L. B., Guillem, J. G., Weiser, M. R., Temple, L. K., Nash, G. M., Paty, P. B., Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy, Annals of Surgery, 256, 965-972, 2012	No multivariate prognostic analysis. Univariate data for: T stage, N stage
Smith, J. J., Chow, O. S., Gollub, M. J., Nash, G. M., Temple, L. K., Weiser, M. R., Guillem, J. G., Paty, P. B., Avila, K., Garcia-Aguilar, J., Rectal Cancer, Consortium, Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management, BMC Cancer, 15, 767, 2015	Protocol for a phase II study.
Smith J, Strombom P, Chow O, et al. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients with a Complete Response after Neoadjuvant Therapy, JAMA Oncology., 2018	No multivariable prognostic analysis
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Appendix L – Research recommendations

Research recommendations for review question: Which people having neoadjuvant radiotherapy or chemoradiotherapy for rectal cancer do not need surgery?

No research recommendations were made for this review question.