Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA report 2017:95

Rectal cancer with complete clinical remission after chemoradiotherapy: resection or watch-and-wait?

Angenete E, Ekelund AC, Hermanson M, Larsson K, Strandell A, Svanberg T, Swartling T, Jivegård L.

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Rectal cancer with complete clinical remission after chemoradiotherapy: resection or watch-and-wait? [Rektalcancer med komplett remission efter kemoradioterapi: operation eller aktiv exspektans?]

Angenete E[1*], Ekelund AC[5], Hermanson M[1], Larsson K[2], Strandell A[3], Svanberg T[4], Swartling T[1], Jivegård L[3]

[1]Department of Surgery, Sahlgrenska University Hospital/Östra, Göteborg, Sweden
[2]Department of Oncology, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden
[3]HTA-centrum of Region Västra Götaland, Sweden.
[4]Medical Library, Sahlgrenska University Hospital, Göteborg, Sweden
[5]Medical Library, Skaraborg Hospital, Lidköping, Sweden

[*]Corresponding author

Published April 2017
2017:95
Suggested citation: Angenete E, Ekelund AC, Hermanson M, Larsson K, Strandell A, Svanberg T, Swartling T, Jivegård L. Rectal cancer with complete clinical remission after chemoradiotherapy: resection or watch-and-wait? [Rektalcancer med komplett remission efter kemoradioterapi: operation eller aktiv exspektans?] Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2017. Regional activity-based HTA 2017:95

Table of contents

1. Abstract

Background

In patients with advanced rectal cancer, chemoradiotherapy is an established treatment to achieve tumour down staging/downsizing prior to surgery and to lower the risk of local recurrence. Approximately 10% of patients have complete clinical response (cCR), i.e. no detectable tumour, after treatment with chemoradiotherapy. For this group of patients a "watch and wait" strategy (W&W) without early resection has been suggested. Rectal resection is associated with significant perioperative risks and complications but also long-term impaired quality of life by altered bowel function.

Objective

To study if it is possible to avoid surgery without compromising disease-free survival in adult patients with rectal cancer planned for curative resection who have had a clinical complete response after initial chemoradiotherapy.

Search methods and study selection criteria

In October 2016 a systematic literature search was conducted in PubMed, Embase, CINAHL, PsycInfo, the Cochrane Library and the CRD database. Two authors independently screened titles, abstracts and full-text articles for inclusion and extracted data. Meta-analyses were conducted when data were possible to pool. The certainty of evidence was defined according to the GRADE system.

Main results

Ten cohort studies were included. The intervention group was rectal cancer patients with cCR after chemoradiotherapy undergoing W&W. Comparison groups were either rectal resection after cCR (C1, four studies) or patients with non-cCR undergoing rectal resection showing no residual tumour in the specimen (pathologicCR) (C2, six studies). The studies included 267 (I) and 356 patients (C1+C2), respectively, and had some or serious study limitations.

Disease-free and overall survival

Disease-free survival was reported in six studies, two with C1 and four with C2. Overall survival was reported in six cohort studies, one with C1 and five with C2. Disease-free survival after five years was not significantly lower (RR 0.93, 95%CI 0.79; 1.09) while overall survival was not different after W&W compared with surgery. Conclusion: It is uncertain whether disease-free survival is lower and whether there is little or no difference in overall survival after W&W compared with surgery (GRADE ⊕◯◯◯).

Distant metastasis

Meta-analysis of ten studies showed that distant metastasis rate was not different after W&W compared with surgery (follow-up 20-72 months). Conclusion: It is uncertain whether there is any difference in the rate of distant metastasis after W&W compared with surgery (GRADE ⊕◯◯◯).

Local recurrence: Meta-analysis of ten studies showed a significantly higher (RR 4.08, 95%CI 2.03; 8.22) local recurrence rate after W&W compared with surgery (follow-up 9.4-60 months). The frequency of local recurrence after W&W across studies varied between 2.8 and 30%. Conclusion: It is uncertain whether W&W compared with surgery increases the local recurrence rate.

Very low certainty of evidence (GRADE ⊕◯◯◯).

Risks and complications

In two cohort studies risks and complications were reported comparing W&W with surgery (C2). There were fewer major complications (RR 0.05, 95%CI 0.01; 0.25) after W&W compared with surgery. Conclusion: It is uncertain whether W&W gives fewer major complications than surgery (GRADE ⊕◯◯◯).

Health related quality of life (HRQoL) was not reported in any study.

Validated bowel Symptom Score

A symptom score was reported in one study with 21 intervention and 20 C2 patients. Bowel function was significantly better after W&W compared with surgery. Conclusion: It is uncertain whether anorectal function is better after W&W compared with surgery (GRADE ⊕◯◯◯).

Concluding remarks

There are only few non-randomised studies including a total of approximately 600 patients of a "watch and wait" strategy compared with surgery in patients with rectal cancer with cCR after chemoradiotherapy. In the studies, survival and the frequency of distant metastasis did not differ while there were more local recurrences and less major complications after "watch and wait", but the certainty of evidence is very low for all outcomes. More studies, particularly on the outcome HRQoL and with adequate follow-up, are needed.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Rektalcancer diagnosticeras hos 1800 personer årligen i Sverige. Behandlingen är kirurgisk och operation (resektion) är förenad med betydande tidig komplikationsrisk och även långsiktiga effekter med nedsatt livskvalitet till följd av stomi och/eller tarmrubbningar. Patienter med mer avancerad rektalcancer får preoperativ kemoradioterapi för att minska tumörens aggressivitet och storlek och därmed sänka risken för lokalrecidiv. Cirka 10% av dessa patienter svarar med komplett remission (cCR) och har ingen kvarvarande tumör efter denna behandling. För dessa patienter används en "watch and wait" strategi (W&W) istället för kirurgi på vissa kliniker i världen.

Syfte
Att studera om W&W jämfört med kirurgisk resektion, hos patienter med rektalcancer som svarar med komplett remission efter kemoradioterapi och planeras för kurativ resektion, inte ger en försämrad överlevnad.

Metod
Under oktober 2016 gjordes systematiska litteratursökningar i PubMed, Embase, CINAHL, PsycInfo, Cochrane Library och CRD databasen. Minst två författare granskade titlar, abstracts och fulltextartiklar, värderade studiekvalitet och extraherade data oberoende av varandra. Resultat och kvalitetsgranskning summerades för varje utfall. När så var möjligt poolades data i meta-analyser. Det vetenskapliga underlagets styrka bedömdes enligt GRADE-systemet.

Resultat
Sökningen resulterade i tio kontrollerade kohortstudier. Interventionsgruppen (patienter med cCR efter kemoradioterapi som genomgått W&W) jämfördes med kontroller som genomgått resektion efter cCR (C1, fyra studier) eller kontroller utan cCR som efter resektion konstaterats ha full remission (ingen kvarvarande tumör) i den bortopererade tarmen (C2, sex studier). Studierna inkluderade 267 (I) respektive 356 (C1+C2) patienter och alla hade vissa eller allvarliga kvalitetsbrister.

Överlevnad rapporterades i sex studier. Sjukdomsfri överlevnad var inte signifikant lägre (RR 0,93, 95% CI 0,79; 1,09) efter W&W jämfört med resektion medan total överlevnad inte skilde sig numeriskt.
Slutsats: Det är osäkert huruvida sjukdomsfri överlevnad är lägre och huruvida det är liten eller ingen skillnad i total överlevnad efter W&W jämfört med resektion (GRADE ⊕◯◯◯).

Fjärrmetastaser: meta-analys av tio studier visade numeriskt ingen skillnad avseende fjärrmetastaser mellan W&W och kirurgi (uppföljning 20-72 månader). Slutsats: Det är osäkert om det föreligger någon skillnad i frekvensen av fjärrmetastaser mellan W&W och resektion (GRADE ⊕◯◯◯).

Lokalrecidiv: meta-analys av tio studier visade fler lokalrecidiv (RR 4,08, 95% CI 2,03; 8,22) efter W&W jämfört med resektion (uppföljning 9,4-60 månader). Frekvensen av lokalrecidiv efter W&W varierade mellan 2,8 och 30 %.
Slutsats: Det är osäkert huruvida W&W ger fler lokalrecidiv än resektion (GRADE ⊕◯◯◯).

Risker och komplikationer rapporterades i två studier jämförande W&W med C2-kontroller. Det var färre allvarliga komplikationer (RR 0,05, 95% CI 0,01; 0,25) efter W&W än efter resektion.
Slutsats: Det är osäkert huruvida det är färre allvarliga komplikationer efter W&W än efter resektion (GRADE ⊕◯◯◯).

Hälsorelaterad livskvalitet rapporterades inte i någon studie.

Validerad symtomskala: avseende tarmsymtom rapporterades i en studie med C2-kontroller. Det var mindre uttalade tarmsymtom efter W&W än efter resektion.
Slutsats: Det är osäkert huruvida det är mindre uttalade tarmsymtom efter W&W jämfört med resektion. (GRADE ⊕◯◯◯).

Sammanfattande kommentar
Det finns ett fåtal kontrollerade kohortstudier inkluderande totalt endast cirka 600 patienter där en "watch and wait" strategi jämförs med rutinmässig resektion hos patienter med avancerad rektalcancer som svarat med full remission på radiokemoterapi. I studierna förelåg ingen signifikant lägre sjukdomsfri överlevnad, färre allvarliga komplikationer samt något högre frekvens lokal recidiv efter "watch and wait" jämfört med kirurgi medan fjärrmetastasering och total överlevnad var liknande i grupperna. Det vetenskapliga stödet är otillräckligt (GRADE ⊕◯◯◯) för samtliga utfall. Fler större kontrollerade studier behövs, särskilt avseende utfallet hälsorelaterad livskvalitet.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2017-02-22

Christina Bergh MD, Professor	Anders Larsson MD, PhD	Henrik Sjövall MD, Professor
Susanne Bernhardsson PT, PhD	Olle Nelzén MD, Associate professor	Petteri Sjögren DDS, PhD
Elisabeth Hansson-Olofsson PhD, Senior lecturer	Christian Rylander MD, PhD	Maria Skogby RN, PhD
Magnus Hakeberg OD, Professor	Ola Samuelsson MD, Associate professor	Annika Strandell MD, Associate professor
Lennart Jivegård MD, Senior university lecturer	Ninni Sernert Associate professor	Therese Svanberg HTA librarian

3. Summary of Findings

Rectal cancer with complete clinical remission after chemoradiotherapy

Comparison of "watch and wait" vs. surgical resection

Outcomes	Study design Number of studies	Relative effect RR (95%CI)[1]	Absolute effect Average[2] (range)	Certainty of evidence GRADE
Disease-free survival	Cohort 3 3	2-3 yrs: 0.91 (0.82; 1.01) 5 yrs: 0.93 (0.79; 1.09)	5 yrs: (62-92% vs 83-94%)	⊕◯◯◯ Very low [3]
Overall survival	Cohort 2 4	2 yrs: 1.02 (0.88; 1.17) 5 yrs: 1.02 (0.89; 1.16)	5 yrs: (71-100% vs 86-96%)	⊕◯◯◯ Very low [4]
Distant metastasis	Cohort 10	0.90 (0.50; 1.60)	6.7% vs 7.6% (0-17% vs 0-14%)	⊕◯◯◯ Very low [5]
Local recurrence	Cohort 10	4.08 (2.03; 8.22)	12.4% vs 2.0% (3-30% vs 0-6%)	⊕◯◯◯ Very low [3]
Major complications	Cohort 2	0.05 (0.01; 0.25)	2.6% vs 48% (0-5% vs 35-57%)	⊕◯◯◯ Very low [6]
Validated symptom score	Cohort 1	-	Improved bowel function	⊕◯◯◯ Very low [7]

Footnotes:

[1] Based on meta-analysis

[2] Calculated on crude numbers in included studies

[3] Downgraded two steps due to serious study limitations (baseline differences in tumour stage and age), some uncertainty about directness (some T2 tumours would not be included according to Swedish guidelines) and uncertain precision.

[4] Downgraded two steps due to serious study limitations (baseline differences in tumour stage and age), some uncertainty about directness (some T2 tumours would not be included according to Swedish guidelines) and serious imprecision.

[5] Downgraded two steps due to serious study limitations (baseline differences in tumour stage and age), some uncertainty about directness (some T2 tumours would not be included according to Swedish guidelines), some inconsistency and uncertain precision.

[6] Downgraded one step due to some study limitations (non-systematic reporting) and serious imprecision.

[7] Downgraded one step due to some limitations (baseline function and length of follow-up not reported) and uncertain precision.

Certainty of evidence

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

4. Abbreviations/Acronyms/Definitions

APE	Abdomino Perineal Excision
cCR	clinical Complete Response
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICTRP	WHO International Clinical Trials Registry Platform (ICTRP)
MRI	Magnetic Resonance Imaging
VGR	Region Västra Götaland
pCR	pathological Complete Response
PET-CT	Positron Emission Tomography – Computed Tomography
RCC	Regionalt Cancer Centrum
RCT	Randomised Controlled Trial
TNM	Tumour Node Metastasis classification developed by the UICC - Union Internationale Contre le Cancer

Definitions

Clinical complete response (cCR) Tumour not detectable on digital examination, endoscopy *and* MRI after treatment. Definitions not including all of the above mentioned methods have also been included in the analysis as information otherwise would be scarce.
Pathological complete response (pCR) No tumour detected in microscopic assessment of surgically resected specimen.
Chemoradiotherapy In this document the term is defined as radiotherapy as basis of treatment with optional addition of chemotherapy.
Follow-up Results in the literature have been reported both as time to actual examination and as estimated future results using calculations in e.g. Kaplan-Meier plots. We have made an effort to report the basis of time to actual follow-up visits for such estimations as means, medians and ranges when available.
Radical surgery In this document rectal resection with free surgical margins.
Disease-free survival (DFS) Patients who have survived and are without detectable tumour at the time of the examination. DFS includes patients who have previously been detected with tumour recurrence, but at follow-up are without detectable tumour after an intervention such as surgery.
Local recurrence Detection of recurrent tumour in the pelvis.
Distant recurrence Detection of recurrent tumour outside the pelvis.
Rectal resection The whole of the rectum or part of the rectum is resected included the whole of or part of the surrounding mesorectum in a standardised fashion (TME-surgery). Rectal resection can be carried out as abdominoperineal resection, low anterior resection including total mesorectal excision or as a high anterior resection including part of the mesorectum. Hartmann's procedure is an anterior resection without anastomosis.
Local excision A rectal tumour is removed with a limited surrounding margin of the wall of the rectum not including the mesorectum.

5. Background

Rectal cancer

Colorectal cancer, adenocarcinoma, is the third most common form of cancer in Sweden causing 750 deaths every year in Sweden. In Sweden there are 6000 new cases of colorectal cancer yearly and 1800 of those are rectal cancers (Regionalt Cancercentrum Väst, http://www.cancercentrum.se/vast/). During the last decades, the prognosis for rectal cancer has improved with decreased risk of local recurrence and increased long term survival (Kodeda et al., 2015). This is probably due to improvements in many areas, including preoperative examinations such as magnetic resonance imaging (MRI), surgical technique, and oncologic diagnostics and treatment.

This health technology assessment was initiated to evaluate treatment of rectal cancer with chemoradiotherapy alone, referred to as the concept of "watch and wait", in patients with clinical complete response (cCR) after chemoradiotherapy.

Prevalence and incidence of rectal cancer

The incidence of rectal cancer in 2007–2011 was 25/100,000 among men and 17/100,000 among women (www.cancercentrum.se). Rectal cancer usually affects the elderly, only 5% of the patients are under age of 50 at time of diagnosis and 23% are over 80 years old. The incidence has remained unchanged over the last decade. More advanced rectal cancer that may be possible to cure, T4 tumours and tumours with threatened surgical margins or other poor prognostic factors are approx10-20% of all rectal cancers yearly.

During 2006-2015, 3,888 patients were diagnosed with ICD C20.9 (malignant tumour in the rectum) or C21.8 (malignant tumour in rectum with infiltration) in Region Västra Götaland (VGR) (Vega, health care database in Region Västra Götaland, containing information regarding all hospital stays at hospitals in Västra Götaland).

Present treatment of rectal cancer

When symptoms of rectal cancer (e.g. hematochezia, anemia and/or altered bowel habits), radiologic findings, or findings at screening are noted, further examinations are performed. These include medical history, digital rectal examination, endoscopy and laboratory tests.

Upon suspicion of rectal cancer, patients are referred to a surgical clinic. Endoscopy is performed including a biopsy of the tumour. Computed tomography of the thorax/abdomen with intravenous contrast, MRI of the pelvis and sometimes transrectal ultrasound are performed. All results are presented and discussed in a multidisciplinary conference (including oncologist, radiologist, colorectal surgeon, liver surgeon, contact nurse). In some cases, PET-CT (Positron Emission Tomography – Computed Tomography) is performed. According to the new standardised referral pathway implemented in Sweden during 2016, the aim is that treatment should start with preoperative treatment such as neoadjuvant chemoradiotherapy or surgery if indicated within 39 days (53 days if extended tumour investigation is needed) after the first suspicion of rectal cancer (Regionalt CancercentrumVäst, http://www.cancercentrum.se/vast/). The addition of neoadjuvant chemoradiotherapy reduces the risk for local recurrence but increases the risk for complications and may affect health-related quality of life (HRQoL) (De Caluwe et al. 2013, Schiffmann et al. 2013). If a patient is treated with chemoradiotherapy there is a possibility that the tumour is undetectable on digital examination, endoscopy and MRI after treatment. This is defined as clinical complete response (cCR).

Surgery for rectal cancer depends on the distance of the tumour from the anal verge. Very low tumours are treated with abdominoperineal excision (APE) rendering the patient with a permanent stoma. Tumours located higher in the rectum can be treated with an anterior resection and a re-establishment of the bowel continuity with an anastomosis, sometimes protected by a temporary stoma (often loop ileostomy).

In early rectal cancer (T1-T3, N0 (according to the tumour classification system TNM version 7) with no involvement of mesorectal margins on MRI) chemoradiotherapy is not standard treatment in Sweden. The relative five-year survival for patients with early rectal cancer stage I (T1-T2, N0) and stage II (T3-T4 N0) treated with standard surgery is 98 and 80%, respectively. The risk for local recurrence is approximately 2-3.4% (RCC 2015). Patients with early rectal cancer who receive chemoradiotherapy have a 40-50% chance of having a cCR after treatment. The “watch and wait” strategy with no surgery has been suggested, and currently several clinical trials are investigating this matter (STAR-TREC, NCT02945566).

In patients with more advanced tumours, regardless of tumour distance from the anal verge, chemoradiotherapy is an established treatment in Sweden to achieve tumour down staging/downsizing prior to surgery (neoadjuvant treatment) and to reduce the risk of local recurrence. There are several reports of patients with more advanced tumours who have achieved cCR after chemoradiotherapy. In these studies, there are case-mixes with selection of patients with less advanced tumours, such as patients with cT1-T2 tumours who would not automatically receive preoperative neoadjuvant treatment in Sweden (Maas et al., 2011). Clinical response is observed in 10-15% of all patients with primary non-resectable or advanced rectal cancer receiving chemoradiotherapy (Hartley et al., 2005, Braendengen et al., 2008, Glynne-Jones 2012). This response rate is believed to increase with the addition of further oncologic treatment (Garcia-Aguilar et al., 2015). Approximately 10-20% of patients with cCR treated with a "watch and wait" strategy will have a local recurrence or regrowth of the tumour within a few years, many of whom can be treated with surgery (Martin et al., 2012). The evaluation of cCR remains difficult, requiring endoscopy, MRI and digital examination. The optimal intervals of follow-up are still not established.

6. Health technology at issue: “Watch and wait” in rectal cancer

Patients with rectal cancer with cCR (no visible tumour on MRI, endoscopy or during digital examination) after chemoradiotherapy are traditionally treated with rectal surgery in Sweden. However, in Brazil and some European countries (Habr-Gama et al., 2004, Maas et al., 2011) the concept of “watch and wait” has been introduced. Patients with cCR are followed closely to monitor if local recurrence/regrowth of tumour occurs. If so, surgery is performed. Patients with cCR planned for “watch and wait” need information about the risk of local regrowth, including the need for an increased number of hospital visits for follow-up, compared with the risks of surgery.

7. Objective

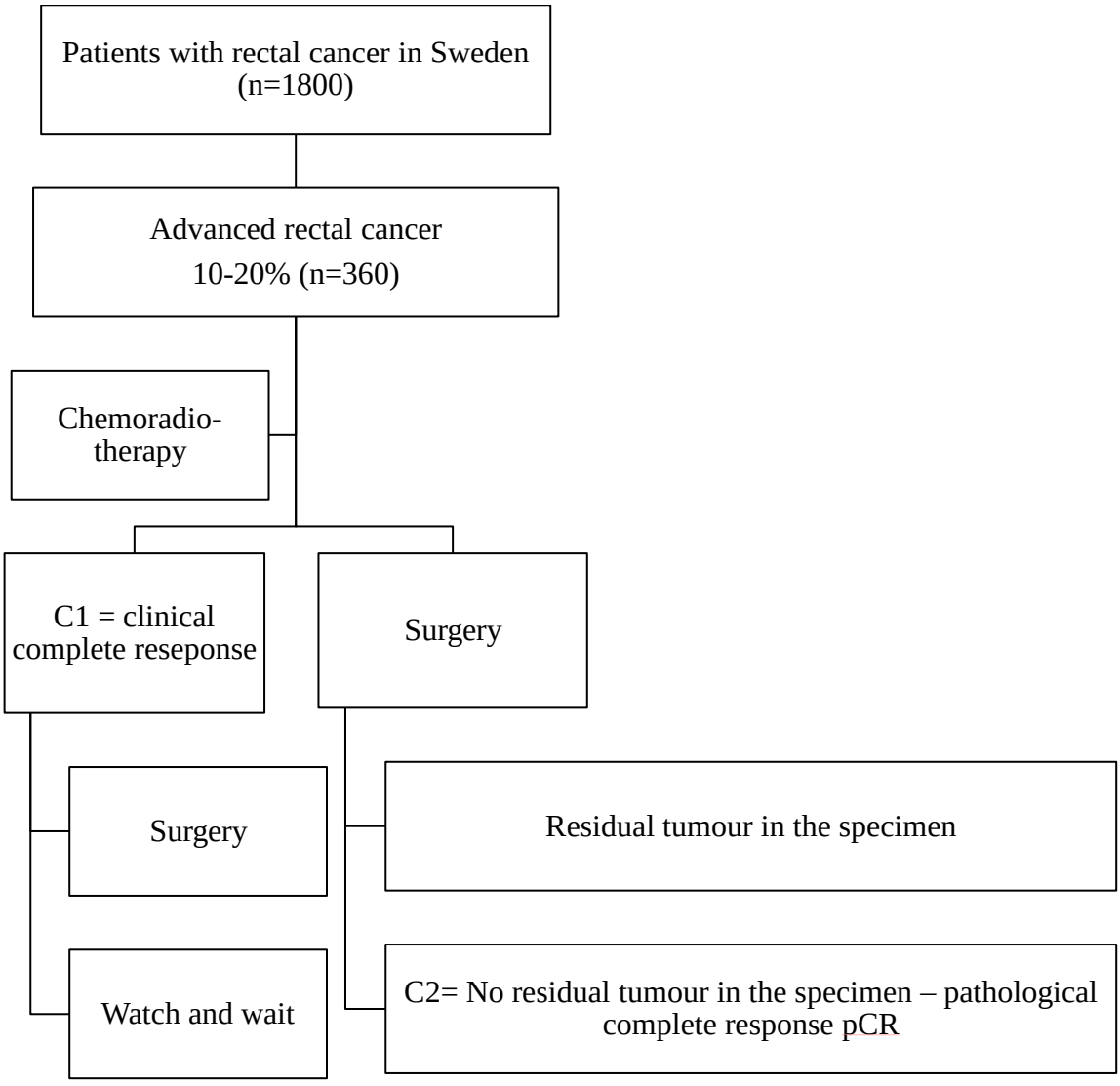
Is it possible to avoid surgery without compromising disease-free survival in adult patients with rectal cancer planned for curative resection who have had a clinical complete response after initial chemoradiotherapy?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P = Adult patients with rectal cancer planned for curative resection with a clinical complete response (cCR) after initial chemoradiotherapy

I = "Watch and wait". In the case of recurrence, surgery if possible.

C = Radical surgery:
C1= Assessed as cCR followed by radical surgery
C2= Radical surgery. No tumour in resected specimen (pCR= pathological complete response).
(Individuals in C2 may not fulfil the P criteria)



O = Critical for decision making
Disease-free survival
Overall survival
Distant metastasis
Local recurrence/residual tumour
Complications
Health-related quality of life

Important but not critical for decision making
Validated symptom score
Surgery due to local recurrence/residual tumour

8. Methods

Systematic literature search (Appendix 1)

During October 2016 two authors (TS, ACE) performed systematic searches in PubMed, Embase, CINAHL, PsycInfo, the Cochrane Library and the Centre for Reviews and Dissemination database. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts, and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another, and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

Included studies, their design and patient characteristics are presented in Appendix 2. Excluded studies and reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using a checklist for assessment of cohort studies, modified from SBU by HTA-centrum. The results and the assessed quality of each article have been summarised per outcome in Appendices 4.1-4.7 Data were extracted by at least two authors per outcome. When possible, data were pooled in meta-analyses using RevMan 5.2 and presented as forest plots. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). The certainty of evidence was defined according to the GRADE system (Atkins et al., 2004).

Ongoing research

A search was performed in Clinicaltrials.gov on 5 December 2016 using the search terms *(non-surgical OR nonsurgical OR non-operative OR nonoperative OR watch-and-wait OR wait-and-watch OR wait-and-see OR watchful waiting)* AND *(rectal cancer OR rectum cancer OR rectal neoplasms).*
A search was performed in WHO International Clinical Trials Registry Platform (ICTRP) 2016-12-05 using the search terms *rectal cancer OR rectum cancer OR rectal neoplasms OR rectum neoplasms* in the title field and *non-surgical OR nonsurgical OR non-operative OR nonoperative OR watch OR wait OR watchful waiting* in the field for condition or intervention.
The retrieved registered studies were checked for eligibility and those fulfilling the PICO criteria are presented in the report.

9. Results

Systematic literature search (Appendix 1)

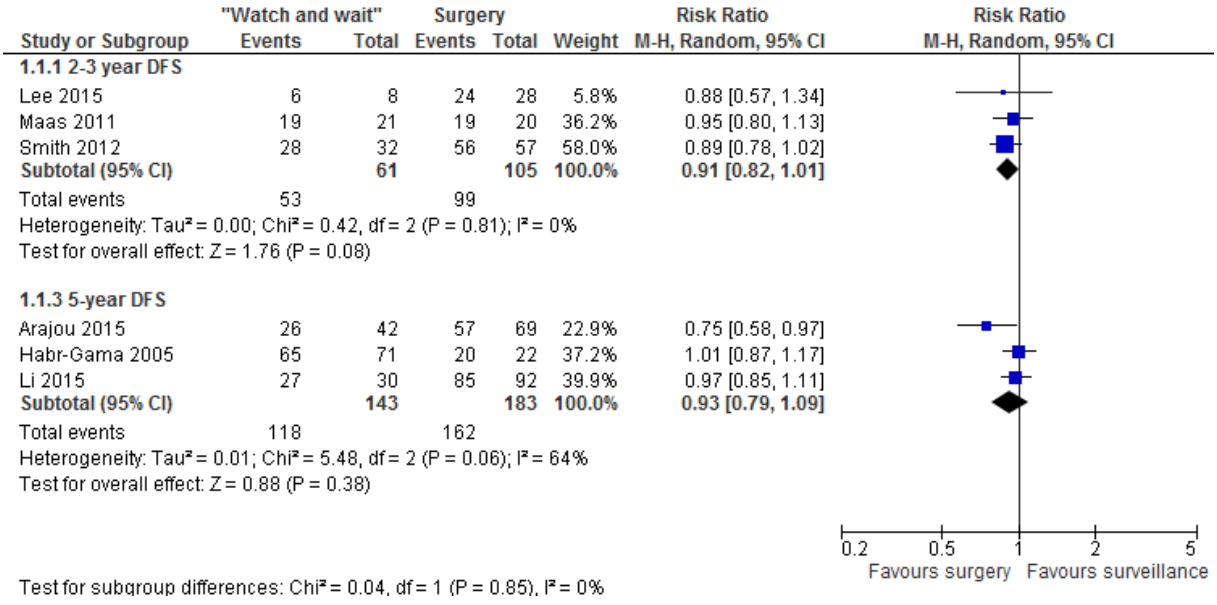
The literature search identified a total of 544 articles after removal of duplicates. After reading the abstracts 473 articles were excluded. Another 33 articles were excluded by two authors (TS, ACE) after reading the articles in full text. The remaining 38 articles were sent to all participants of the project group, and ten articles (one RCT and nine non-randomised controlled cohort studies) were finally included in the assessment (Appendix 2). The small RCT study population (n=6) was part of a prospective cohort study and results were very sparsely reported. The study was in this report handled as a cohort study (assessment with checklist and included in meta-analyses with the other non-randomised studies).

Outcomes critical for decision-making

Disease-free survival (Appendix 4.1)

Disease-free survival was reported in six cohort studies, comparing the intervention "watch and wait" after cCR with surgery (C1) or comparing "watch and wait" after cCR with pCR after surgery (C2). There were two studies (124 patients) in control group 1 and four (164 patients) in control group 2. The studies had major limitations. Disease-free survival was not significantly lower in the "watch and wait" groups compared with surgery groups with a follow-up of 2-3 and five years respectively including a total of 492 patients (Figure 1).

Fig.1 Meta-analysis of studies comparing "watch and wait" with surgery
Outcome: Disease-free survival

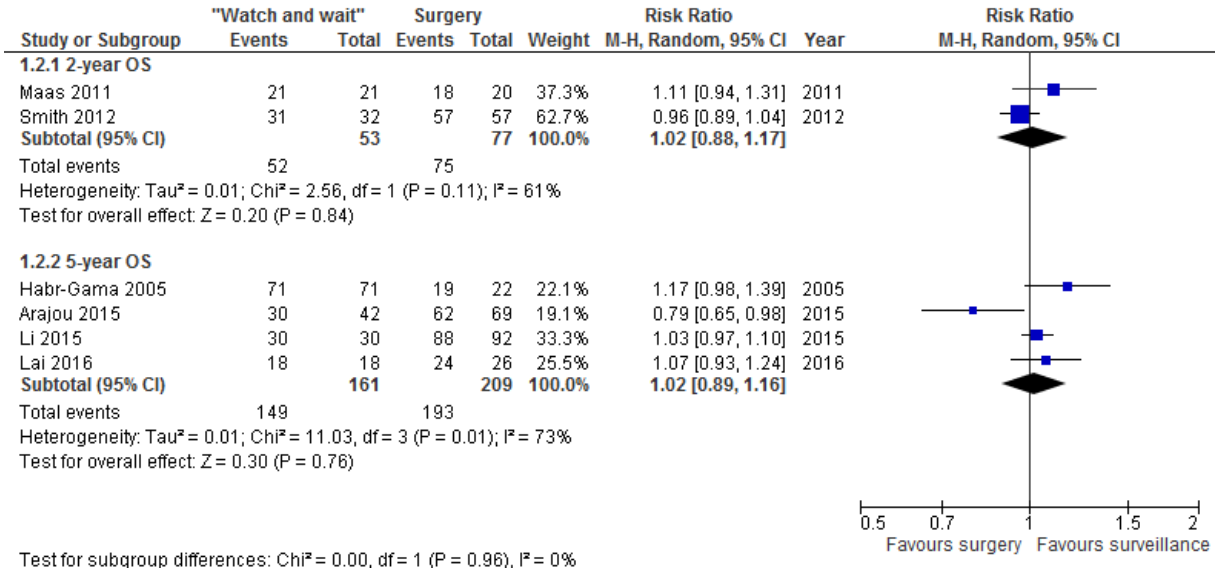


Conclusion: It is uncertain whether there is any difference in disease-free survival between "watch and wait" and surgery in rectal cancer patients with complete response after chemoradiotherapy alone. Very low certainty of evidence (GRADE ⊕◯◯◯).

Overall survival (Appendix 4.2)

Overall survival was reported in six cohort studies, comparing the intervention "watch and wait" after cCR with surgery (C1) or comparing "watch and wait" after cCR with pCR after surgery (C2). There was one study (92 patients) in control group 1 and five (121 patients) in control group 2. The studies had major limitations. Overall survival did not differ between the "watch and wait" groups and the surgery groups with a follow-up of two and five years respectively, including a total of 500 patients (Figure 2).

Fig.2 Meta-analysis of studies comparing "watch and wait" with surgery
Outcome: Overall survival

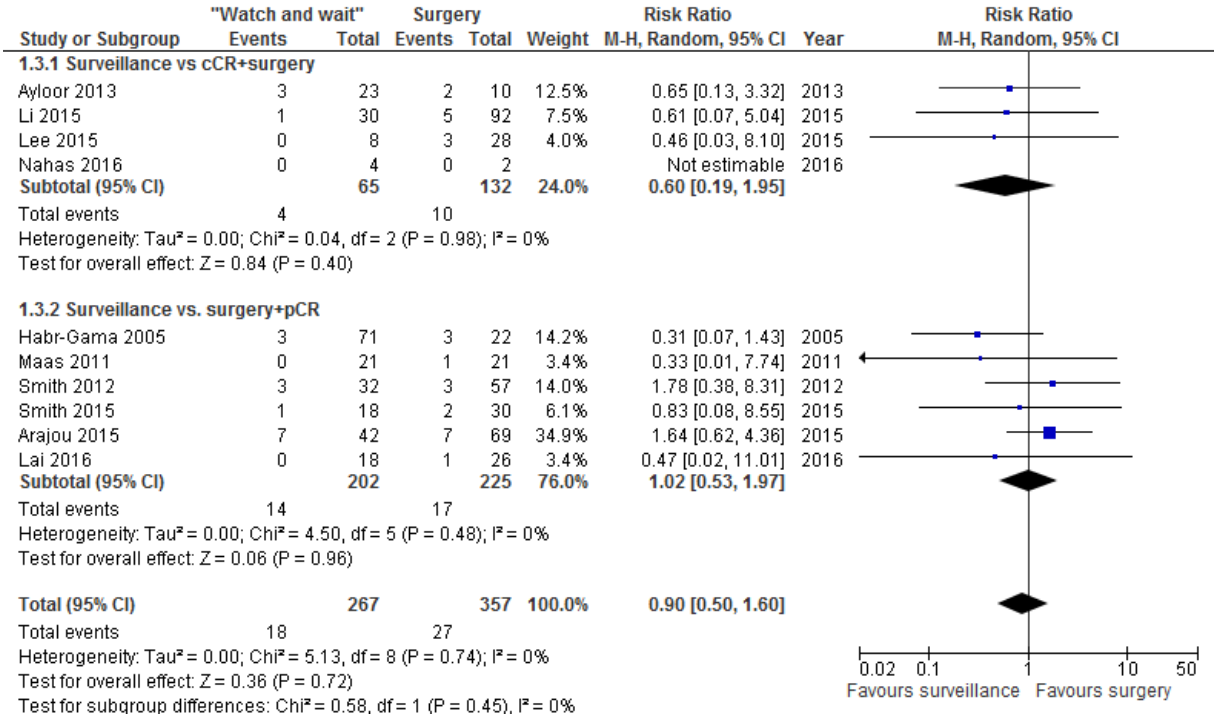


Conclusion: It is uncertain whether there is any difference in long-term survival between "watch and wait" and surgery in rectal cancer patients with complete response to chemoradiotherapy alone. Very low certainty of evidence (GRADE ⊕◯◯◯).

Distant metastasis (Appendix 4.3)

Distant metastasis was reported in ten cohort studies, comparing the intervention "watch and wait" after cCR with surgery (C1) or comparing "watch and wait" after cCR with pCR after surgery (C2). The studies had major limitations. The reported distant metastasis rate did not differ between the "watch and wait" groups and the surgery groups; the pooled RR of ten studies was 0.90 with a 95% CI of 0.50 to 1.60, including 624 patients (Figure 3). The mean duration of follow-up varied between 20 and 50 months.

Fig.3 Meta-analysis of studies comparing "watch and wait" with surgery
Outcome: Distant metastasis.

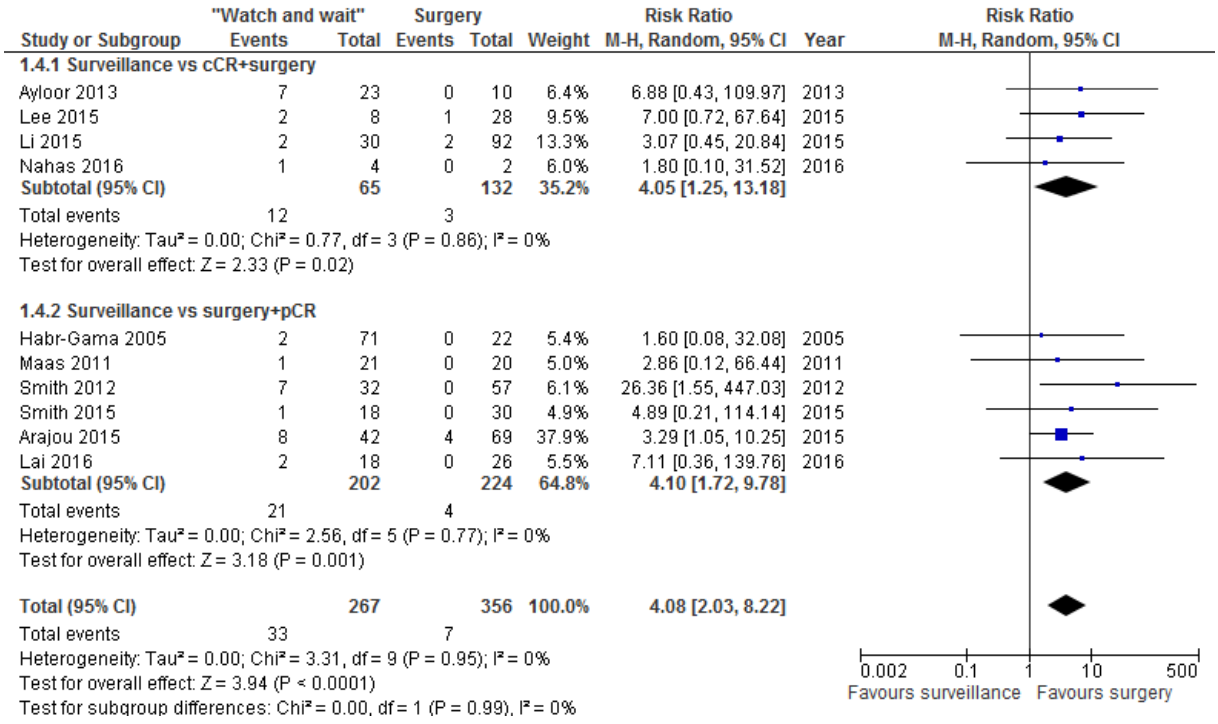


Conclusion: It is uncertain whether there is any difference in the rate of distant metastasis between "watch and wait" and surgery in rectal cancer patients with complete response after chemoradiotherapy alone. Very low certainty of evidence (GRADE ⊕◯◯◯).

Local recurrence/residual tumour (Appendix 4.4)

Local recurrence was reported in ten cohort studies, comparing the intervention "watch and wait" after cCR with surgery (C1) or comparing "watch and wait" after cCR with pCR after surgery (C2), in patients with rectal cancer. The studies had major limitations and the level of evidence was down-graded due to selection bias. The reported local recurrence rate was higher in the "watch and wait" groups than in the surgery groups; the pooled RR of ten studies was 4.08 with a 95% CI of 2.03 to 8.22, including 623 patients with a mean follow-up of 9-60 months (Figure 4).

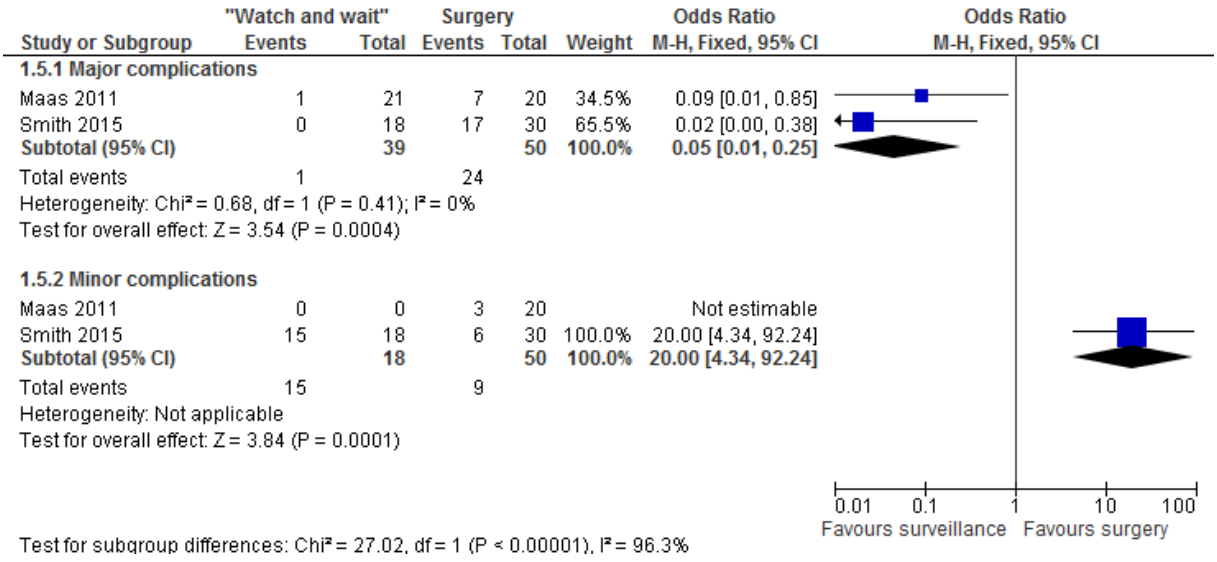
Fig.4 Meta-analysis of studies comparing "watch and wait" with surgery
Outcome: Local recurrence/residual tumour



Conclusion: It is uncertain whether "watch and wait" is associated with a higher local recurrence rate in rectal cancer patients with cCR after chemoradiotherapy, compared with surgery.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Complications (Appendix 4.5)
Complications were reported in two cohort studies, comparing the intervention "watch and wait" after cCR with pCR after surgery (C2) for patients with rectal cancer. The studies had major limitations. Reports regarding side effects of chemoradiotherapy were scarce, but major surgical complications (that can only be found if surgery has been performed), such as anastomotic leakage and abscesses, were reported in 16/30 patients in one study and in 7/20 in the other study. The pooled RR of two studies was 0.05 with a 95% CI of 0.01 to 0.25, including 89 patients (Figure 5). The groups are not comparable in evaluating complications, since surgical complications have only been reported in two of ten included studies, and the long-term complications due to chemoradiotherapy in non-operated patients have not been described at all.

Fig.5 Meta-analysis of studies comparing "watch and wait" with surgery
Outcome: Complications



Conclusion: Major surgical complications are common. It is uncertain whether major complications are less frequent after "watch and wait" than after surgery in rectal cancer patients with complete response to chemoradiotherapy. Very low certainty of evidence (GRADE ⊕◯◯◯).

Health related quality of life was not reported in any study.

Outcomes, important for decision-making

Validated Symptom Score (Appendix 4.6)
A validated symptom score for anorectal function was reported in one cohort study, comparing the intervention "watch and wait" after cCR with pCR after surgery (C2), for 21 vs 20 patients with rectal cancer. The study had major limitations. The patient reported anorectal function was improved after "watch and wait" compared with surgery.
Conclusion: It is uncertain whether anorectal function is improved after "watch and wait" compared with surgery in rectal cancer patients with complete response to chemoradiotherapy.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Surgery due to local recurrence/residual tumour (Appendix 4.7)
Results are similar to those of the outcome Local recurrence (Appendix 4.1) and are not further commented on. Details of surgical procedures are given in Appendix 4.7.

10. Ethical issues

It is possible that avoidance of surgery could improve quality of life in patients with rectal cancer and cCR after chemoradiotherapy. Still this will probably only be possible for 10-20% of patients with advanced rectal cancer (n=200 patients yearly), in Sweden approximately at most 30-40 patients per year. It is possible that this treatment could have a positive effect as it may reduce complications and improve functional outcome and the established treatment today, surgery, is afflicted with a high risk of complications and functional impairment.

However, long-term outcome remains uncertain and there is insufficient scientific evidence to recommend this treatment outside trials. The treatment also requires patient compliance with regular out-patient visits and follow-up with MRI. Due to patient compliance requirements, all patients cannot be offered this treatment. Moreover it may not be possible to offer this treatment at every hospital in Sweden due to competence requirements in the radiology and surgical departments. Currently the treatment has many unknown outcomes and it is not possible to give the patients accurate information regarding long term survival and recurrence results.

Treatment with "watch and wait" after chemoradiotherapy is probably less resource consuming than chemoradiotherapy followed by surgery. Still, as the number of recurrences or regrowth and patient requiring further treatment is unknown it is uncertain whether this will be cost saving for the society.

11. Organisational aspects

Time frame for the putative introduction of the new health technology
The "watch and wait" strategy can be implemented into Swedish health care without much delay. However, there is a need for educational efforts both for surgeons and radiologists, to ascertain adequate evaluations of complete response after treatment. It will most probably not be possible to implement this strategy at every hospital treating rectal cancer due to the limited number of patients eligible for "watch and wait". Concentrating treatment of patients eligible for "watch and wait" to a few centres in Sweden is probably the most efficient way to achieve and retain competence, but on the other hand this will require patients to travel across Sweden regularly. The timing of radiologic evaluation after oncological treatment (chemoradiotherapy) needs to be modified and probably delayed for a few weeks compared with current standards. Outpatient visits will increase slightly as the patients will be under surveillance at least four times a year the first two to five years after their treatment.

Present use of the technology in other hospitals in Region Västra Götaland
"Watch and wait" is not considered standard follow-up and is not used in Region Västra Götaland. At Karolinska University Hospital in Stockholm, 15-20 patients have been followed up using the"watch and wait" strategy.

Consequences of the new health technology for personnel
There will be a need for continuous training of physicians in order to make sure of correct evaluation of cCR, residual tumour and regrowth. Endoscopists may be involved initially to help in the clinical evaluation of cCR but it is probable that mainly colorectal surgeons with knowledge of the disease and additional treatment will be treating the patients.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland
The method will involve all clinics treating patients with rectal cancer in Region Västra Götaland. All patients with a tumour requiring chemoradiotherapy alone are currently reviewed in a multidisciplinary regional board and it is suggested that patients presenting with possible cCR after treatment should be referred to Sahlgrenska University Hospital/Östra for further evaluation.

12. Economic aspects

Present cost of currently used technologies
There are approximately 35 patients per year, diagnosed with malignant tumour in the rectum (ICD C20.9), or malignant tumour in rectum with infiltration (C21.8) who are treated with neoadjuvant chemoradiotherapy alone and surgery in Region Västra Götaland. The cost per patient for neoadjuvant chemoradiotherapy alone is 53,500 SEK at the Sahlgrenska University hospital. In addition to this cost, three visits to the physician and one visit with medical tests per week during a period of five weeks are estimated to a cost of 10,000 SEK per patient. Thus, the annual total cost for neoadjuvant chemoradiotherapy alone is estimated to be 2.2 million SEK for 35 patients. The cost per patient for surgery was 225,000 SEK (average during 2014-2016) at the Sahlgrenska University hospital. The annual total cost for surgery is estimated to be 7.9 million SEK for 35 patients. The total annual cost for neoadjuvant chemoradiotherapy alone and surgery is estimated to be 10 million SEK.

Expected costs of the new health technology
At most there will be an addition of 10-15 patients yearly that will be possible to follow-up with the "watch and wait" strategy in Region Västra Götaland. The cost per patient for only the neoadjuvant chemoradiotherapy alone was 63,500 SEK, corresponding to 635,000 to 952,500 SEK per year for these patients. However, this will require more outpatient visits including flexible endoscopy. This will require 80-90 additional outpatient visits and 60 additional MRI scans yearly, estimated to an additional annual cost of 1.6 million SEK. The total annual cost is estimated to be 2.3-2.6 million SEK.

Total change of cost
There will be savings of costs as approximately 10-15 patients will not be subjected to an abdominoperineal resection, a procedure that requires six to eight hours of operating time, six to eight days of hospital stay and is afflicted with a complication rate of 30-40%. The cost savings are estimated to the cost of the surgery for 10-15 patients, i.e. 2.2-3.4 million SEK. With the additional annual cost for the new health technology of 1.6 million SEK, the total cost savings are estimated to 630,000 SEK to 1.8 million SEK.

However, there will be new costs with increased surveillance of rectal cancer patients. As it is unknown if the long-term risk for surgery decreases with the "watch and wait" strategy, it is not possible to calculate the costs within the first five years after start of the treatment.

Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?
The colorectal unit at Sahlgrenska University Hospital/Östra is a tertiary referral centre and will require funding for the additional MRI and outpatient visits that will be required to provide adequate surveillance of the patients.

Available analyses of health economy or cost advantages or disadvantages
No health economic evaluations of this technique have yet been published.

13. Discussion

This systematic review/health technology assessment deals with the approximately 10-20% of all patients with advanced rectal cancer. These patients have responded to treatment with cCR after having received chemoradiotherapy and may be candidates for a “watch and wait” strategy rather than routine early surgery. The identified studies included in this report all had study limitations and were of small sample sizes. There was a case-mix with a clear selection with less advanced tumours included such as cT1-T2 tumours, which would not automatically receive neoadjuvant treatment in Sweden (Maas et al., 2011).
Clinical complete response has varying definitions in the literature. A common definition is lack of signs of tumour using palpation, endoscopy and MRI. Even with this definition, results of assessment is uncertain and subject to bias. Due to these limitations, the report findings are uncertain and results of the meta-analyses must be interpreted with great caution.

If patients with cCR after chemoradiotherapy are treated with a “watch and wait” strategy, 2-25% will have local tumour regrowth within a couple of years after treatment and the recurrence rate is likely to increase with longer follow-up. Local recurrence is known to have a large impact on the patient’s quality of life, but how this will affect patients previously treated with “watch and wait” is not known (Camilleri-Brennan et al., 2001). The drawbacks of routine early surgery in these patients are mainly a rather high rate of complications associated with surgery. Some of these complications are early and severe while others impair long-term bowel function.

The results of salvage surgery for recurrence after a “watch and wait” strategy are uncertain.

Distant metastases are a common cause of death for a patient with rectal cancer. However, these patients may sometimes be treated with surgery provided prompt detection and treatment. Whether the “watch and wait” policy will have an adverse effect on this outcome remains uncertain. Patients with cCR to chemoradiotherapy have a better prognosis, compared with patients that did not respond as well to their neoadjuvant treatment, if they are subjected to surgery (Maas et al., 2010, Martin et al., 2012) but whether surgery is required to keep their good prognosis is not known. This is why the studies reviewed in this report have been performed.

Long-term survival remains the most important outcome. The current data do not suggest any differences in disease-free or overall survival, but the certainty of evidence is very low.

Functional outcome after rectal cancer surgery affects health related quality of life, but whether the “watch and wait” approach will improve functional outcome is uncertain although the present data suggested a lower risk for functional impairment, but the certainty of evidence was very low. Complications after surgery for rectal cancer are common (30-40%) and may have a negative effect on health-related quality of life (Hornbrook et al., 2011). It is likely that older patients may benefit more from a "watch and wait" strategy, in which they have a possibility to completely avoid the serious complications from surgery (Smith et al., 2015).

There are a few previous reviews dealing with this topic (Martin et al., 2012, Li et al., 2016). The present HTA report adds a systematic review and quality assessment of all available controlled studies and is in agreement with the previously published reviews that a watch and wait strategy seems feasible, but that selection and long term results are uncertain due to the low scientific quality of included studies.

14. Future perspective

Scientific knowledge gaps

There is lack of evidence regarding which patients will achieve a cCR, how follow-up should be done and the outcome in patients with tumour regrowth during "watch and wait". The patient's Quality of Life and experiences of surveillance and functional outcome have not been investigated. It is important to compare the patient's QoL between surgery (and inherent complications) and W&W (with inherent long follow-up).

There is a need for further studies within this field. Preferably a randomised controlled trial should be performed, comparing a "watch and wait" strategy with surgery in patients with rectal cancer who have achieved a cCR after chemoradiotherapy. Such a study is probably not feasible, as the number of patients is low. However, a controlled study of quality of life study would be possible and is urgent. A prospective register study should be feasible to study disease-free and overall survival.
It is theoretically possible that time to recurrence is delayed after clinical complete response. Therefore follow-up needs to be longer than the median two to five year follow-up in the present studies.

Ongoing research

The searches in Clinical Trials and WHO and ICTRP identified 108 and 53 trials respectively. After removal of duplicates 145 (108 + 37) trials were reviewed and only one fulfilled the PICO criteria.

- NCT01047969, Royal Marsden, UK (completed recruitment, planning on including 99 patients, started 2006 and preliminary completed June 2019). The study includes patients with locally invasive high-risk rectal adenocarcinoma that present with no viable disease on MRI 4 weeks after completion of chemoradiotherapy. The primary endpoint is the percentage of patients who can safely omit surgery two years after completion of treatment with no surgery and who are in cCR without local disease.

Other registered studies of interest are listed below.

One study is exploring the functional outcome after chemoradiotherapy and "watch and wait" strategy, but may include other patients than those defined in the PICO of the present HTA report:

- NCT02278653, Maastrichts University Medical Center, Netherlands.

Ten studies include patients that would not have been given full chemoradiotherapy alone in Sweden, thus they do not fulfil our PICO for all patients in the study:

- NCT02008656, Bejing Cancer Hospital, China,
- ChiCTR-TRC-12002488, Beijing Cancer Hospital, China
- NCT02860234, Memorial Slone Kettering, USA
- NCT02052921, Instituto Do Câncer Do Estado de São Paulo, Brazil
- NCT01047969, University of Padova, Italy
- NCT02945566, University of Birmingham, UK
- EUCTR2016-000862-49-NL, University of Birmingham, UK
- NCT00952926, Vejle Hospital, Denmark
- NCT02438839, Vejle Hospital, Denmark,
- NCT01863862, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Poland

In one study, it is difficult to fully explore if patients would have received chemoradiotherapy alone in Sweden, thus if they include patients outside the PICO in the HTA report:

- NCT00939666, Maastrichts University Medical Center, Netherlands.

15. Participants in the project

The question was nominated by

Eva Angenete, Associate professor, consultant colorectal surgeon, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Participating health care professionals

Eva Angenete, MD, Associate professor, consultant colorectal surgeon, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital/Östra, Göteborg, Sweden. E-mail: eva.angenete@vgregion.se

Maria Hermanson, MD, PhD-student, Resident in Surgery, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Karolina Larsson, MD, Resident in Oncology, Oncology Department, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden

Torbjörn Swartling, MD, Ph.D., consultant colorectal surgeon, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Participants from the HTA-centrum

Lennart Jivegård, MD, Associate professor, HTA-centrum of Region Västra Götaland, Sweden
Annika Strandell, MD, Associate professor, HTA-centrum of Region Västra Götaland, Sweden
Josefin Persson, Health economist, HTA-centrum of Region Västra Götaland, Sweden
Therese Svanberg, HTA librarian, HTA-centrum of Region Västra Götaland, Sweden
Ann-Catrin Ekelund, Librarian, Skaraborg Hospital, Lidköping, Region Västra Götaland, Sweden

External reviewers

Michael Breimer, Professor, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Andreas Hallqvist, MD, Ph. D., Department of Oncology, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden

Declaration of interest

The authors declare no conflict of interest.

Project time

HTA was accomplished during the period of 2016-09-21 – 2017-02-22.
Literature searches were made in October 2016.

Appendix 1, Search strategy, study selection and references

Question(s) at issue:
Is it possible to avoid surgery without compromising disease-free survival in adult patients with rectal cancer planned for curative resection who have had a clinical complete response after initial chemoradiotherapy?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P = Adult patients with rectal cancer planned for curative resection with a clinical complete response (cCR) after initial chemoradiotherapy

I = "Watch and wait". In the case of recurrence, surgery if possible.

C = Radical surgery:
C1: Assessed as cCR followed by radical surgery
C2: Radical surgery. No tumour in resected specimen (pCR= pathological complete response). (Individuals in C2 may not fulfil the P criteria)

O = <u>Critical for decision making</u>
Disease-free survival
Overall survival
Distant metastasis
Local recurrence/residual tumour
Complications
Health-related quality of life

<u>Important but not critical for decision making</u>
Validated symptom score
Surgery due to local recurrence/residual tumour

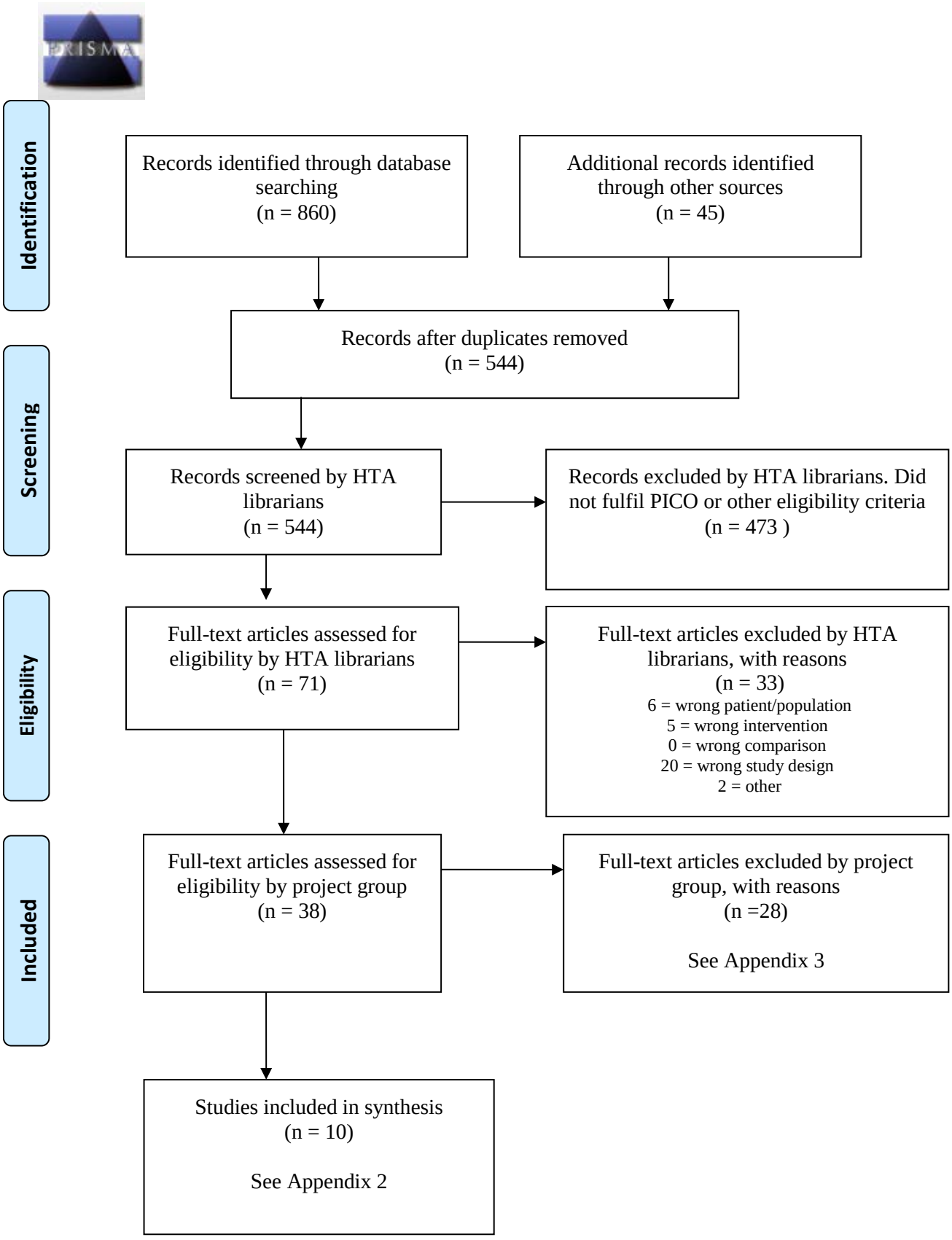
<u>Eligibility criteria</u>

Study design:
RCT
Non-randomised controlled studies

Language:
English, Swedish, Norwegian, Danish

Publication date: -

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2016-10-03
No of results: 374

Search	Query	Items found
#33	**Search #27 NOT #30 Filters: Swedish; Norwegian; English; Danish**	**374**
#31	Search #27 NOT #30	424
#30	Search #29 OR #28	5707208
#29	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1508445
#28	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4257883
#27	Search #23 AND #26	454
#26	Search #24 OR #25	37032
#25	Search non-surgical[tiab] OR nonsurgical[tiab] OR non-operative[tiab] OR nonoperative[tiab] OR watch-and-wait[tiab] OR wait-and-watch[tiab] OR wait-and-see[tiab] OR watchful waiting[tiab]	35405
#24	Search "Watchful Waiting"[Mesh]	2069
#23	Search #19 OR #22	68139
#22	Search #20 AND #21	51189
#21	Search rectal[tiab] OR rectum[tiab]	96991
#20	Search cancer[tiab] OR carcinom*[tiab] OR neoplas*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR sarcom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR lesion*[tiab] OR malign*[tiab]	3202219
#19	Search "Rectal Neoplasms"[Mesh]	41074

Database: EMBASE (OVID SP)
Date: 2016-10-03
No of results: 385

#	Searches	Results
1	rectum cancer/ or exp rectum carcinoma/	37442
2	rectum tumor/ or exp rectum adenoma/ or exp rectum polyp/	18639
3	(rectal or rectum).ab,ti.	130322
4	(cancer or carcinom* or neoplas* or tumor or tumors or tumour or tumours or sarcom* or adenocarcinom* or adeno-carcinom* or adenom* or lesion* or malign*).ab,ti.	4044655
5	3 and 4	73471
6	1 or 2 or 5	90144
7	exp watchful waiting/	3102
8	((wait adj2 watch) or (wait adj2 see) or (watchful adj2 waiting)).ab,ti.	5363
9	(non-surgical or nonsurgical or non-operative or nonoperative).ab,ti.	39567
10	7 or 8 or 9	46252
11	6 and 10	708
12	limit 11 to ((danish or english or norwegian or swedish) and (article or conference paper or note or "review"))	385
13	(animal not (animal and human)).sh.	1320503
14	**12 not 13**	**385**

Database: CINAHL + PsycInfo (EBSCO)
Date: 2016-10-03
No of results: 54

#	Searches	Results
S7	**S3 AND S6**	**54**
S6	S4 OR S5	5407
S5	TI (non-surgical or nonsurgical or non-operative or nonoperative) OR AB (non-surgical or nonsurgical or non-operative or nonoperative)	4815
S4	TI (((wait N2 watch) OR (wait N2 see) OR (watchful N2 waiting))) OR AB (((wait N2 watch) OR (wait N2 see) OR (watchful N2 waiting)))	605
S3	S1 AND S2	2252
S2	TI (cancer or carcinom* or neoplas* or tumor or tumors or tumour or tumours or sarcom* or adenocarcinom* or adeno-carcinom* or adenom* or lesion* or malign*) OR AB (cancer or carcinom* or neoplas* or tumor or tumors or tumour or tumours or sarcom* or adenocarcinom* or adeno-carcinom* or adenom* or lesion* or malign*)	207215
S1	TI (rectal OR rectum) OR AB (rectal OR rectum)	4,443

Database: The Cochrane Library
Date: 2016-10-03
No of results: 29
Cochrane reviews 5
Other reviews 1
Technology assessments
Economic evaluations 1
Clinical trials 22

ID	Search	Hits
#1	MeSH descriptor: [Rectal Neoplasms] explode all trees	1371
#2	rectal or rectum:ti,ab,kw (Word variations have been searched)	8644
#3	cancer or carcinom* or neoplas* or tumor or tumors or tumour or tumours or sarcom* or adenocarcinom* or adeno-carcinom* or adenom* or lesion* or malign*:ti,ab,kw (Word variations have been searched)	133220
#4	#2 and #3	4044
#5	#1 or #4	4120
#6	MeSH descriptor: [Watchful Waiting] explode all trees	222
#7	((wait near/2 watch) or (wait near/2 see) or (watchful near/2 waiting)):ti,ab,kw (Word variations have been searched)	668
#8	non-surgical or nonsurgical or non-operative or nonoperative:ti,ab,kw (Word variations have been searched)	2533
#9	#6 or #7 or #8	3179
#10	**#5 and #9**	**29**

Database: CRD database
Date: 2016-10-03
No of results: 18

ID	Search	Hits
1	(rectal OR rectum)	863
2	(cancer or carcinom* or neoplas* or tumor or tumors or tumour or tumours or sarcom* or adenocarcinom* or adeno-carcinom* or adenom* or lesion* or malign*)	15329
3	#1 AND #2	534
4	(non-surgical or nonsurgical or non-operative or nonoperative)	595
5	(((wait NEAR2 watch) or (wait NEAR2 see) or (watchful NEAR2 waiting)))	160
6	#4 OR #5	744
7	**#3 AND #6**	**18**

Reference lists
A comprehensive review of reference lists brought 45 new records

---

Reference lists

Included studies:

Araujo RO, Valadao M, Borges D, Linhares E, de Jesus JP, Ferreira CG, et al. Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study. Eur J Surg Oncol. 2015;41(11):1456-63.

Ayloor Seshadri R, Kondaveeti SS, Jayanand SB, John A, Rajendranath R, Arumugam V, et al. Complete clinical response to neoadjuvant chemoradiation in rectal cancers: can surgery be avoided? Hepatogastroenterology. 2013;60(123):410-4.

Habr-Gama A, Perez RO, Nadalin W, Nahas SC, Ribeiro U, Jr., Silva ESAH, Jr., et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. J Gastrointest Surg. 2005;9(1):90-9; discussion 9-101.

Lai CL, Lai MJ, Wu CC, Jao SW, Hsiao CW. Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait". Int J Colorectal Dis. 2016;31(2):413-9.

Lee SY, Kim CH, Kim YJ, Kim HR. Oncologic Outcomes according to the Treatment Strategy in Radiologic Complete Responders after Neoadjuvant Chemoradiation for Rectal Cancer. Oncology. 2015;89(6):311-8.

Li J, Liu H, Yin J, Liu S, Hu J, Du F, et al. Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study. Oncotarget. 2015;6(39):42354-61.

Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29(35):4633-40.

Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF, Ribeiro U, Jr., Cotti GC, Imperiale AR, et al. 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. Dis Colon Rectum. 2016;59(4):255-63.

Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg. 2012;256(6):965-72.

Smith RK, Fry RD, Mahmoud NN, Paulson EC. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. Int J Colorectal Dis. 2015;30(6):769-74.

Excluded studies:

Abrams MJ, Koffer PP, Leonard KL. The Emerging Non-operative Management of Non-metastatic Rectal Cancer: A Population Analysis. Anticancer Res. 2016;36(4):1699-702.

Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015;16(8):919-27.

Bhangu A, Kiran RP, Audisio R, Tekkis P. Survival outcome of operated and non-operated elderly patients with rectal cancer: A Surveillance, Epidemiology, and End Results analysis. Eur J Surg Oncol. 2014;40(11):1510-6.

Bitterman DS, Resende Salgado L, Moore HG, Sanfilippo NJ, Gu P, Hatzaras I, et al. Predictors of Complete Response and Disease Recurrence Following Chemoradiation for Rectal Cancer. Front Oncol. 2015;5:286.

Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw. 2014;12(4):513-9.

Ellis CT, Samuel CA, Stitzenberg KB. National Trends in Nonoperative Management of Rectal Adenocarcinoma. J Clin Oncol. 2016;34(14):1644-51.

Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. Br J Surg. 2012;99(7):897-909.

Glynne-Jones R, Hughes R. Complete Response after Chemoradiotherapy in Rectal Cancer (Watch-and-Wait): Have we Cracked the Code? Clin Oncol (R Coll Radiol). 2016;28(2):152-60.

Habr-Gama A. Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. Colorectal Dis. 2006a;8:21-4.

Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88(4):822-8.

Habr-Gama A, Lynn PB, Jorge JM, Sao Juliao GP, Proscurshim I, Gama-Rodrigues J, et al. Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. Dis Colon Rectum. 2016;59(4):264-9.

Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr., et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711-7; discussion 7-8.

Habr-Gama A, Perez RO, Proscurshim I, Campos FG, Nadalin W, Kiss D, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg. 2006b;10(10):1319-28; discussion 28-9.

Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum. 2009;52(12):1927-34.

Habr-Gama A, Perez RO, Sao Juliao GP, Proscurshim I, Gama-Rodrigues J. Nonoperative approaches to rectal cancer: a critical evaluation. Semin Radiat Oncol. 2011;21(3):234-9.

Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56(10):1109-17.

Lambregts DM, Lahaye MJ, Heijnen LA, Martens MH, Maas M, Beets GL, et al. MRI and diffusion-weighted MRI to diagnose a local tumour regrowth during long-term follow-up of rectal cancer patients treated with organ preservation after chemoradiotherapy. Eur Radiol. 2016;26(7):2118-25.

Li J, Li L, Yang L, Yuan J, Lv B, Yao Y, et al. Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. Oncotarget. 2016;0.

Martens MH, Maas M, Heijnen LA, Lambregts DM, Leijtens JW, Stassen LP, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. J Natl Cancer Inst. 2016;108(12).

Moureau-Zabotto L, Resbeut M, Gal J, Mineur L, Teissier E, Hebuterne X, et al. Management and clinical outcome of rectal cancer in patients >/= 80 years treated in southern France (PACA region) between 2006 and 2008. J Surg Oncol. 2013;108(7):450-6.

Nakagawa WT, Rossi BM, de OFF, Ferrigno R, David Filho WJ, Nishimoto IN, et al. Chemoradiation instead of surgery to treat mid and low rectal tumors: is it safe? Ann Surg Oncol. 2002;9(6):568-73.

Neuman HB, Elkin EB, Guillem JG, Paty PB, Weiser MR, Wong WD, et al. Treatment for patients with rectal cancer and a clinical complete response to neoadjuvant therapy: a decision analysis. Dis Colon Rectum. 2009;52(5):863-71.

Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016;17(2):174-83.

Rossi BM, Nakagawa WT, Novaes PE, Filho WD, Lopes A. Radiation and chemotherapy instead of surgery for low infiltrative rectal adenocarcinoma: a prospective trial. Ann Surg Oncol. 1998;5(2):113-8.

Rupinski M, Szczepkowski M, Malinowska M, Mroz A, Pietrzak L, Wyrwicz L, et al. Watch and wait policy after preoperative radiotherapy for rectal cancer; management of residual lesions that appear clinically benign. Eur J Surg Oncol. 2016;42(2):288-96.

Smith FM, Rao C, Oliva Perez R, Bujko K, Athanasiou T, Habr-Gama A, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum. 2015;58(2):159-71.

Smith FM, Waldron D, Winter DC. Rectum-conserving surgery in the era of chemoradiotherapy. Br J Surg. 2010;97(12):1752-64.

Vaccaro CA, Yazyi FJ, Ojra Quintana G, Santino JP, Sardi ME, Beder D, et al. Locally advanced rectal cancer: Preliminary results of rectal preservation after neoadjuvant chemoradiotherapy. Cir Esp. 2016;94(5):274-9.

Other references:

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490-4.

Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008;26(22):3687-94.

Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2001;27(4):349-53.

[Checklist from SBU regarding cohort studies. (Modified) Version 2010:1]. [Internet]. [cited 2016 Dec 14] Available from: https://www2.sahlgrenska.se/upload/SU/HTAcentrum/Hj%c3%a4lpmedel%20under%20projektet/B03_Granskningsmall%20f%c3%b6r%20kohortstudier%20med%20kontrollgrupp%202014-10-29.doc

De Caluwe L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev. 2013(2):Cd006041.

Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957-66.

Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. The British journal of surgery. 2012;99(7):897-909.

GRADE Working Group. [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2017 Jan 31]. Available from: http://www.gradeworkinggroup.org

Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr., et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Annals of surgery. 2004;240(4):711-7; discussion 7-8.

Hartley A, Ho KF, McConkey C, Geh JI. Pathological complete response following pre-operative chemoradiotherapy in rectal cancer: analysis of phase II/III trials. The British journal of radiology. 2005;78(934):934-8.

Hornbrook MC, Wendel CS, Coons SJ, Grant M, Herrinton LJ, Mohler MJ, et al. Complications among colorectal cancer survivors: SF-6D preference-weighted quality of life scores. Med Care. 2011;49(3):321-6.

Kodeda K, Johansson R, Zar N, Birgisson H, Dahlberg M, Skullman S, et al. Time trends, *improvements* and national auditing of rectal cancer management over an 18-year period. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2015;17(9):O168-79.

Li J, Li L, Yang L, Yuan J, Lv B, Yao Y, et al. Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. Oncotarget. 2016.

Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29(35):4633-40.

Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835-44.

Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. British Journal of Surgery. 2012;99(7):918-28.

RCC. Rektalcancer Nationell kvalitetsrapport för år 2015 fr an Svenska Kolorektalcancerregistret. 2015.

Schiffmann L, Wedermann N, Gock M, Rau B, Klar E, Prall F, et al. Intensified neoadjuvant radiochemotherapy for rectal cancer enhances surgical complications. BMC Surg. 2013;13(1):43.

Smith FM, Rao C, Oliva Perez R, Bujko K, Athanasiou T, Habr-Gama A, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum. 2015;58(2):159-71.

Report: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 2 Included studies – design and patient characteristics.

Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Nahas, 2016, Brazil	RCT	2	I = W&W after cCR C1 = surgery after cCR	6	**	**	Local recurrence Distant metastasis
Araujo, 2015, Brazil	Cohort Retrospective	11	I = W&W after cCR C2 = pCR after surgery	111	61	46%	Local recurrence Distant metastasis Disease-free survival Overall survival
Ayloor, 2013, India	Cohort Retrospective	17	I = W&W after cCR C1 = surgery after cCR	33	52	61%	Local recurrence Distant metastasis
Habr-Gama, 2005, Brazil	Cohort Prospective	11	I = W&W after cCR C2 = pCR after surgery	93	56	52%	Local recurrence Distant metastasis Disease-free survival Overall survival
Lai, 2016, China	Cohort Retrospective	7	I = W&W after cCR C2 = pCR after surgery	44	66	61%	Local recurrence Distant metastasis Overall survival
Lee, 2015, Korea	Cohort Retrospective	5	I = W&W after cCR C1 = surgery after cCR	36*	65	78%	Local recurrence Distant metastasis Disease-free survival
Li, 2015, China	Cohort Prospective	7	I = W&W after cCR C2 = pCR after surgery	122	***	64%	Local recurrence Distant metastasis Disease-free survival Overall survival
Maas, 2011, The Netherlands	Cohort Prospective	6	I = W&W after cCR C2 = pCR after surgery	41	65	73%	Local recurrence Distant metastasis Disease-free survival Overall survival Complications Health-related quality of life

Report: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 2 Included studies – design and patient characteristics.

Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Smith, 2012, USA	Cohort Retrospective	4	I = W&W after cCR C2 = pCR after surgery	89	64	51%	Local recurrence Distant metastasis Disease-free survival Overall survival
Smith, 2015, USA	Cohort Retrospective	12	I = W&W after cCR C2 = pCR after surgery	48	61	73%	Local recurrence Distant metastasis Complications

W&W = watch and wait. cCR = clinical complete response. pCR = pathological complete response.

* Sixteen patients were excluded because they were treated with local excision instead of radical surgery.

** Not specified in the study.

*** Mean age is not reported. Median age is 62 in the intervention group and 56 in the control group.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 3. Excluded studies

Study author, publication year	Reason for exclusion
Abrams, 2016	Not concurrent with PICO, case series.
Appelt, 2015	Not concurrent with PICO, case series. The patients did not receive long time radiochemotherapy and are not planned for surgery.
Bhangu, 2014	Not concurrent with PICO, the P is not met. No report on how many patients that had complete response before surgery.
Bitterman, 2015	Not concurrent with PICO, different aim. Examines predictors for complete response.
Cercek, 2014	Not concurrent with PICO, different aim. No outcomes reported regarding control group.
Ellis, 2016	Not concurrent with PICO, not the outcome we are interested in.
Glynne-Jones, 2012	Not concurrent with PICO, systematic review.
Glynne-Jones, 2016	Not concurrent with PICO, systematic review.
Habr-Gama, 2006a	Not concurrent with PICO, case-series.
Habr-Gama, 2006b	Not concurrent with PICO, case-series.
Habr-Gama, 2016	Not concurrent with PICO, the C is not met. Not radical resection.
Habr-Gama, 2013	Not concurrent with PICO, case series.
Habr-Gama, 2014	Not concurrent with PICO, case series.
Habr-Gama, 2011	Not concurrent with PICO, case series.
Habr-Gama, 2009	Not concurrent with PICO, the C is not met, control group not complete response.
Habr-Gama, 2004	Double publication with Habr-Gama 2005.
Lambregts, 2016	Not concurrent with PICO, wrong aim (value of MRI). Wrong control group.
Li, 2016	Not concurrent with PICO, the C is not met. Complete vs near complete vs surgery. Systematic review.
Martens, 2016	Not concurrent with PICO, case series.
Moureau-Zabotto, 2013	Not concurrent with PICO, the C is not met, the population cannot be identified. Complete response not reported.
Nakagawa, 2002	Not concurrent with PICO, the C is not met. Wrong control group – incomplete response.
Neuman, 2009	Decision analysis article. No additional data presented.
Renehan, 2016	Not concurrent with PICO, case series.
Rossi, 1998	Case series.
Rupinski, 2016	Not concurrent with PICO, the C is not met.
Smith, 2015	No new data. Patients from other studies.
Smith, 2010	Not concurrent with PICO, systematic review.
Vaccaro, 2016	Not concurrent with PICO, the C is not met.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.1
Outcome variable: Disease-free survival

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Araujo, 2015, Brazil	Cohort Retrospective	n = 111 I = 42 C2 = 69	not specified	5 years survival 60.9%		5 years survival 82.8%	not specified	?	-	-
Habr-Gama, 2005, Brazil	Cohort Prospective	n = 93 I = 71 C2 = 22	not specified	5 years survival 92%		5 years survival 83%	I = 80% T3-T4 C = 96% T3-T4	?	-	-
Lee, 2015, Korea	Cohort Retrospective	n = 36 I = 8 C1 = 28	I = 0 C1 = 0	3 years survival 75%	3 years survival 85%		T3N1 or <5 cm > T2N0	?	-	-
Li, 2015, China	Cohort Prospective	n = 122 I = 30 C1 = 92	I = 0 C1 = 0	27/30 (90%) 5 years p = 0.912	85/92 (94.3%) 5 years		I = 23% T3 C = 53% T3	?	?	-
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	2 years survival 89% 95% CI 43; 98% log rank p = 0.77		2 years survival 93% 95% CI 59; 99%	I = 67% T3 C = 80% T3	?	?/-	-
Smith, 2012, USA	Cohort Retrospective	n = 89 I = 32 C2 = 57	I = 0 C2 = not specified	28/32 (88%) 2 years p=0.27		56/57 (98%) 2 years	I = 69% T3 C = 78% T3	?	-	-

RCT = Randomised controlled trial, I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response
T = tumour stage, N = lymph nodes involved.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.2
Outcome variable: Overall survival

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Araujo, 2015, Brazil	Cohort Retrospective	n = 111 I = 42 C2 = 69	not specified	5 years survival 71.6%		5 years survival 89.9%	not specified	?	-	-
Habr-Gama, 2005, Brazil	Cohort Prospective	n = 93 I = 71 C2 = 22	not specified	5 years survival 100%		5 years survival 88%	I = 80% T3-T4 C = 96% T3-T4	?	-	-
Lai, 2016, Taiwan	Cohort Retrospective	n =44 I = 18 C2 = 26	not specified	5 years survival 100%		5 years survival 92.3%	Stadium II-III. Not separated between groups.	+	?	-
Li, 2015, China	Cohort Prospective	n = 122 I = 30 C1 = 92	I = 0 C1 = 0	5 years survival 100% p = 0.912	5 years survival 95.6%		I = 23% T3 C = 53% T3	?	?	-
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	2 years survival 100%		2 years survival 91% 95% CI 59 – 99% log rank p = 0.23	I = 67% T3 C = 80% T3	?	?/-	-
Smith, 2012, USA	Cohort Retrospective	n = 89 I = 32 C2 = 57	I = 0 C2 = not specified	2 years survival 97% p=0.56		2 years survival 100%	I = 69% T3 C = 78% T3	?	-	-

RCT = Randomised controlled trial, I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response
T = tumour stage, N = lymph nodes involved.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.3
Outcome variable: Distant metastasis

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Nahas, 2016, Brazil	RCT Retrospective	n = 6 I = 4 C1 = 2	I = 0 C1 = 0	0/4 mean 31.8 months	0/2 mean 31.8 months		T2N1-T3N2	+	?	-
Araujo, 2015, Brazil	Cohort Retrospective	n = 111 I = 42 C2 = 69	not specified	7/42 (16.7%) mean 23.5 months		7/69 (10.1%) median 24.2 months	not specified	?	-	-
Ayloor, 2013, India	Cohort Retrospective	n = 33 I = 23 C1 = 10	I = 3 C1 = 1	3/23 (6%) median 72 months	2/10 (3.6%) median 37 months		T3N1 or <5 cm >T2N0	?	?	-
Habr-Gama, 2005, Brazil	Cohort Prospective	n = 93 I = 71 C2 = 22	not specified	3/71 (4.2%) mean 52 months		3/22 (13.6%) mean 21 months	I = 80% T3-T4 C = 96% T3-T4	?	-	-
Lai, 2016, Taiwan	Cohort Retrospective	n =44 I = 18 C2 = 26	not specified	0/18 mean 49.9 months p = 0.27		1/26 (3.8%) 14 months	Stadium II-III. Not separated between groups.	+	?	-
Lee, 2015, Korea	Cohort Retrospective	n = 36 I = 8 C1 = 28	I = 0 C1 = 0	0/8 median follow-up 41 months	3/28 (10.7%) median follow-up 41 months		T3N1 or <5 cm > T2N0	?	-	-
Li, 2015, China	Cohort Prospective	n = 122 I = 30 C1 = 92	I = 0 C1 = 0	1/30 (3.3%) 50 months p = 0.912	5/92 (5.4%) mean 49 months		I = 23% T3 C = 53% T3	?	?	-
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	0/21 mean 25 months		1/20 (5%) 3 years	I = 67% T3 C = 80% T3	?	?/-	-
Smith, 2012, USA	Cohort Retrospective	n = 89 I = 32 C2 = 57	I = 0 C2 = not specified	3/32 (8.0%) mean 20 months p=0.30		3/57 (5.3%) median 25 months	I = 69% T3 C = 78% T3	?	-	-
Smith, 2015, USA	Cohort Retrospective	n = 48 I = 18 C2 = 30	not specified	1/18 (5.6%) 32 months		1/30 (3.3%) 23 months	I = 88% T3 C = 83% T3	?	-	-

RCT = Randomised controlled trial, I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response
T = tumour stage, N = lymph nodes involved.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.4
Outcome variable: Local recurrence/residual tumour

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Nahas, 2016, Brazil	RCT Retrospective	n = 6 I = 4 C1 = 2	I = 0 C1 = 0	1/4 (25.0%) mean 31.8 months	0/2 mean 31.8 months		T2N1-T3N2	+	?	-
Araujo, 2015, Brazil	Cohort Retrospective	n = 111 I = 42 C2 = 69	not specified	8/42 (19.0%) mean 24.2 months		4/69 (5.8%) median 24.2 months	not specified	?	-	-
Ayloor, 2013, India	Cohort Retrospective	n = 33 I = 23 C1 = 10	I = 3 C1 = 1	7/23 (30.4%) median 12 months	0/10 median 37 months		T3N1 or <5 cm >T2N0	?	?	-
Habr-Gama, 2005, Brazil	Cohort Prospective	n = 93 I = 71 C2 = 22	not specified	2/71 (2.8%) mean 60 months		0/22 mean 48 months	I = 80% T3-T4 C = 96% T3-T4	?	-	-
Lai, 2016, Taiwan	Cohort Retrospective	n =44 I = 18 C2 = 26	not specified	2/18 (11.1%) mean 50 months p = 0.27		0/26 mean 42.3 months	Stadium II-III. Not separated between groups.	+	?	-
Lee, 2015, Korea	Cohort Retrospective	n = 36 I = 8 C1 = 28	I = 0 C1 = 0	2/8 (25%) median 41 months	1/28 (3.6%) median FU 41 months		T3N1 or <5 cm > T2N0	?	-	-
Li, 2015, China	Cohort Prospective	n = 122 I = 30 C1 = 92	I = 0 C1 = 0	2/30 (6.7%) mean 22 months p = 0.912	2/92 (2.2%) mean 27 months		I = 23% T3 C = 53% T3	?	?	-
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	1/21 (4.8%) 22 months		0/20 mean 35 months	I = 67% T3 C = 80% T3	?	?/-	-
Smith, 2012, USA	Cohort Retrospective	n = 89 I = 32 C2 = 57	I = 0 C2 = not specified	7*/32 (21%) median 11 months p < 0.001		0/57 median 43 months	I = 69% T3 C = 78% T3 *6-7. Unclear reporting.	?	-	-
Smith, 2015, USA	Cohort Retrospective	n = 48 I = 18 C2 = 30	not specified	1/18 (5.6%) 9.4 months		0/30 46.3 months	I = 88% T3 C = 83% T3	?	-	-

All studies reported local recurrence and not residual tumour.
RCT = Randomised controlled trial, I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response
T = tumour stage, N = lymph nodes involved.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.5
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	1/21 * (4.8%) unclear reporting ** mean follow-up 25 months		7/20 * (35%) 3/20 ** (15%) mean follow-up 35 months	I = 67% T3 C = 80% T3	?	?/-	-
Smith, 2015, USA	Cohort Retrospective	n = 48 I = 18 C2 = 30	not specified	0/18 * 15/18 ** (83%) average follow-up 68.4 months		17/30 * (56.7%) 6/30 ** (20%) average follow-up 46.3 months	Tumour stage: I = 88% T3 C = 83% T3	?	-	-

RCT = Randomised controlled trial, I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response
T = tumour stage, N = lymph nodes involved.
* Major complications such as anastomotic leakage, abscess, respiratory failure.
** Minor complications such as urinary retention, wound infection, diarrhoea.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.6
Outcome variable: Validated symptom score

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	Changed bowel habits 47 * p = 0.043 Use of pads 0 * Flatus control ** p = 0.036 Urgency 18 * <u>Wexner incontinence score:</u> mean 0.8 p = 0.182 <u>Defecation frequency:</u> mean 1.8/d p = 0.323		Changed bowel habits 100 * Use of pads 32 * p = 0.045 Flatus control 32 * Urgency 50 * <u>Wexner incontinence score:</u> mean 3.5 <u>Defecation frequency:</u> mean 2.8/d	I = 67% T3 C = 80% T3 Mean follow up: I = 25 months, C2 = 35 months Sloan-Kettering bowel function instrument * Proportion estimated from figure ** Not reported Wexner score 0-20. Lowest score implies perfect continence.	?	?/-	-

I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response, T = tumour stage, N = lymph nodes involved.

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.7
Outcome variable: Surgery due to local recurrence/residual tumour

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Nahas, 2016, Brazil	RCT from a cohort study	n = 6 I = 4 C1 = 2	I = 0 C1 = 0	1 TME/4 (25%) 6 months	0/2 mean 31.8 months		T2N1-T3N2	+	?	-
Araujo, 2015, Brazil	Cohort Retrospective	n = 111 I = 42 C2 = 69	not specified	4 TME/42 (9.5%) median 24.2 months		0/69 median follow-up 46.7 months	not specified	?	-	-
Ayloor, 2013, India	Cohort Retrospective	n = 33 I = 23 C1 = 10	I = 3 C1 = 1	5 TME/23 (21.7%) median 12 months	0/10 median 37 months		T3N1 or <5 cm >T2N0	?	?	-
Habr-Gama, 2005, Brazil	Cohort Prospective	n = 93 I = 71 C2 = 22	not specified	1 LE/71 (1.4%) 56 months		0/22 mean 48 months	I = 80% T3-T4 C = 96% T3-T4	?	-	-
Lai, 2016, Taiwan	Cohort Retrospective	n =44 I = 18 C2 = 26	not specified	2 LE/18 (11.1%) mean 25 months		0/26 42.3 months	Stadium II-III. Not separated between groups.	+	?	-
Lee, 2015, Korea	Cohort Retrospective	n = 36 I = 8 C1 = 28	I = 0 C1 = 0	1 TME/8 (12.5%) median follow-up 41 months	0/28 median follow-up 41 months		T3N1 or <5 cm > T2N0	?	-	-
Li, 2015, China	Cohort Prospective	n = 122 I = 30 C1 = 92	I = 0 C1 = 0	1 TME/30 1 LE/30 (6.7%) mean 22 months	1 TME/92 1 LE/92 (2.2%) mean 27 months		I = 23% T3 C = 53% T3	?	?	-
Maas, 2011, The Netherlands	Cohort Prospective	n = 41 I = 21 C2 = 20	I = 0 C2 = 0	1 LE/21 (4.8%) 22 months		0/20 mean follow-up 35 months	I = 67% T3 C = 80% T3	?	?/-	-

Project: Rectal cancer with complete clinical remission after chemoradiotherapy
Appendix 4.7
Outcome variable: Surgery due to local recurrence/residual tumour

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawls - dropouts	Results			Comments Tumour stage	* Directness	* Study limitations	* Precision
				Intervention (I) cCR + watch and wait	Control 1 (C1) cCR + surgery	Control 2 (C2) Surgery + pCR				
Smith, 2012, USA	Cohort Retrospective	n = 89 I = 32 C2 = 57	I = 0 C2 = not specified	6 TME/32 (18.8%) median 11 months		0/57 median follow-up 43 months	I = 69% T3 C = 78% T3	?	-	-
Smith, 2015, USA	Cohort Retrospective	n = 48 I = 18 C2 = 30	not specified	1 TME/18 (5.6%) 9.4 months		0/30 average 46.3 months	I = 88% T3 C = 83% T3	?	-	-

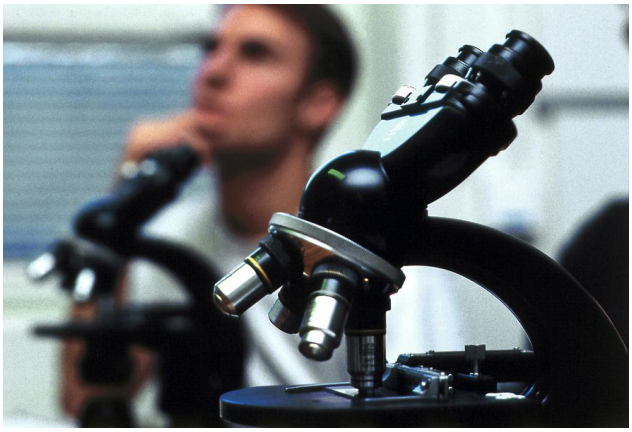
RCT = Randomised controlled trial, I = Intervention, C = Control, C1 includes cCR = clinical complete response, C2 includes pCR = pathological complete response, T = tumour stage, N = lymph nodes involved, TME = total mesorectal excision (radical resection), LE = local excision.

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/hta-centrum

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

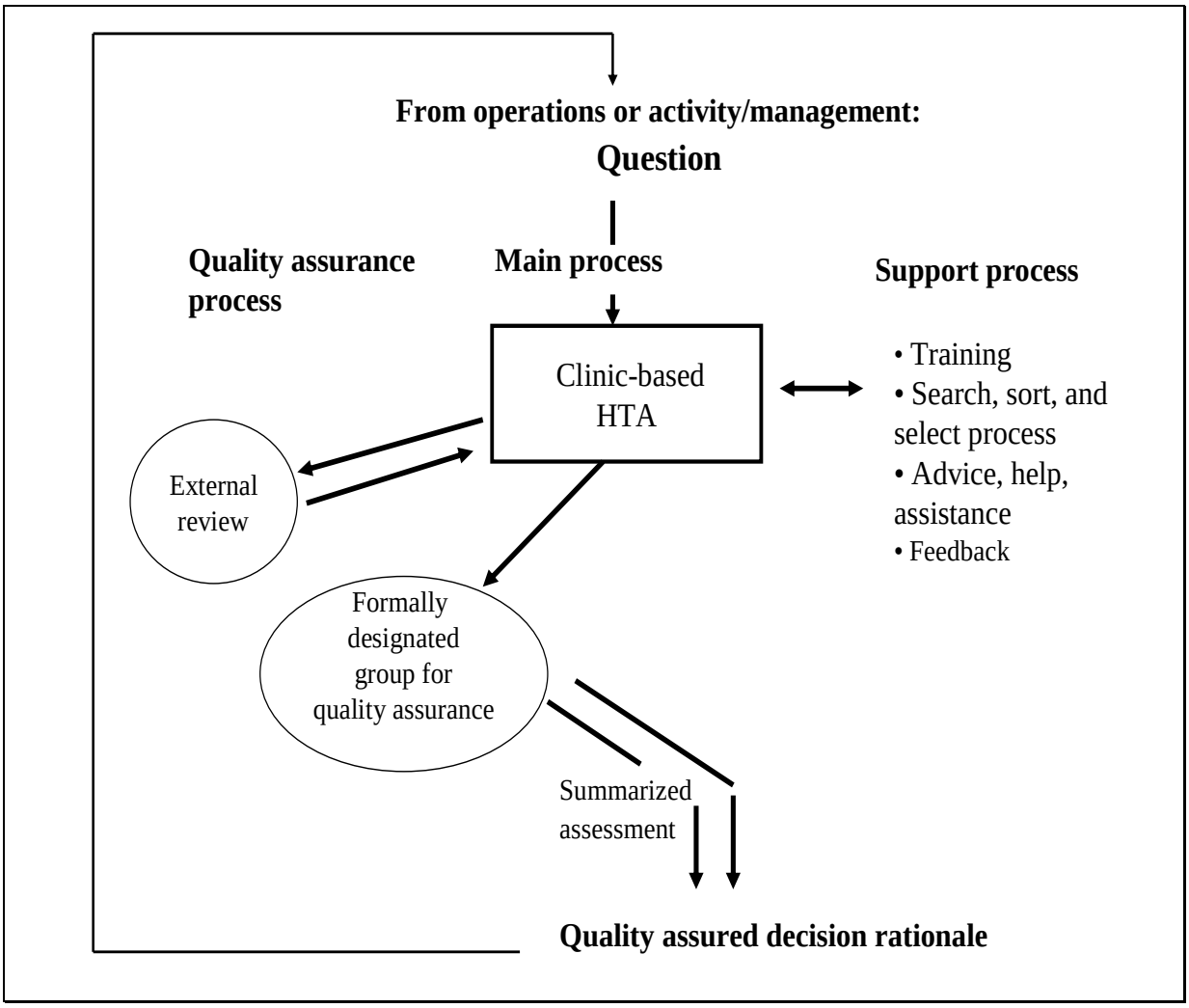
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale