

# Systematic review report for question NEO1a

## Clinical Question NEO1:

Which patients with rectal cancer stage I-II could be considered for definitive chemoradiotherapy (no surgery), neoadjuvant chemoradiotherapy or surgery alone?

- a) What is the optimal timing for surgery after neoadjuvant therapy?
- b) Should they be restaged?

## PICO NEO1-a:

*For patients diagnosed with stage I-III rectal cancer, for which patients does neoadjuvant treatment (short or long course chemoradiotherapy) with surgery achieve equivalent or better outcomes in terms of length and quality of life than neoadjuvant chemoradiotherapy alone?*

Population	Intervention	Comparator	Outcomes	Study Design
Patients diagnosed with stage I-III rectal cancer	- Definitive neoadjuvant chemoradiotherapy	- Neoadjuvant chemoradiotherapy with surgery	- Rectal cancer mortality - 30-day mortality - Distant metastases - Disease-free survival - Overall survival - Local recurrence - Quality of life - Sexual dysfunction - Adverse events - Rehospitalisation - Permanent stoma formation - Return to normal bowel function	- Level III-2 cohort studies and non-randomised trials

## 1. Methods

### 1.1. Guidelines

Relevant recent guidelines (2005 onwards) were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (<http://guideline.gov/>) and the Guidelines Resource Centre ([www.cancerview.ca](http://www.cancerview.ca)).

To be considered for adoption guidelines had to meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (<http://www.agreetrust.org/resource-centre/agree-ii/>).

### 1.2. Literature Search

PubMed (01/01/2004 to 31/08/2016), Embase (01/01/2004 to 31/08/2016), CINAHL (01/01/2004 to 31/08/2016), PsycINFO (01/01/2004 to 31/08/2016), Cochrane Database of Systematic Reviews (01/01/2004 to 31/08/2016), Database of Abstracts of Reviews of Effects and Health Technology Assessment databases (01/01/2004 to 31/08/2016) were searched using text terms and, where available, database specific subject headings.

Each database was searched for articles dealing with colorectal cancer. In PubMed, Embase, CINAHL and PsycINFO databases, the colorectal cancer search was coupled with diagnostic interval search terms. To identify studies which considered Aboriginal and Torres Strait Islanders (ATSI) these searches were then coupled with search terms for ATSI. A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all relevant articles were checked for potential additional relevant articles.

## Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	- Level III-2 cohort studies and non-randomised trials	
Population	- Patients diagnosed with stage I-III rectal cancer	-Patients with distant metastases M1 -Patients diagnosed with rectosigmoid cancer -Palliative treatment studies
Intervention	- Definitive neoadjuvant chemoradiotherapy	-Adjuvant/postoperative chemoradiotherapy
Comparator	- Neoadjuvant chemoradiotherapy with surgery	
Outcomes	- Rectal cancer mortality - 30-day mortality - Distant metastases - Disease-free survival - Overall survival - Local recurrence - Quality of life - Sexual dysfunction - Adverse events - Rehospitalisation - Permanent stoma formation - Return to normal bowel function	
Language	English	
Publication period	From 01/01/2004 to 31/08/2016	

## 2. Results

### 2.1. Guidelines

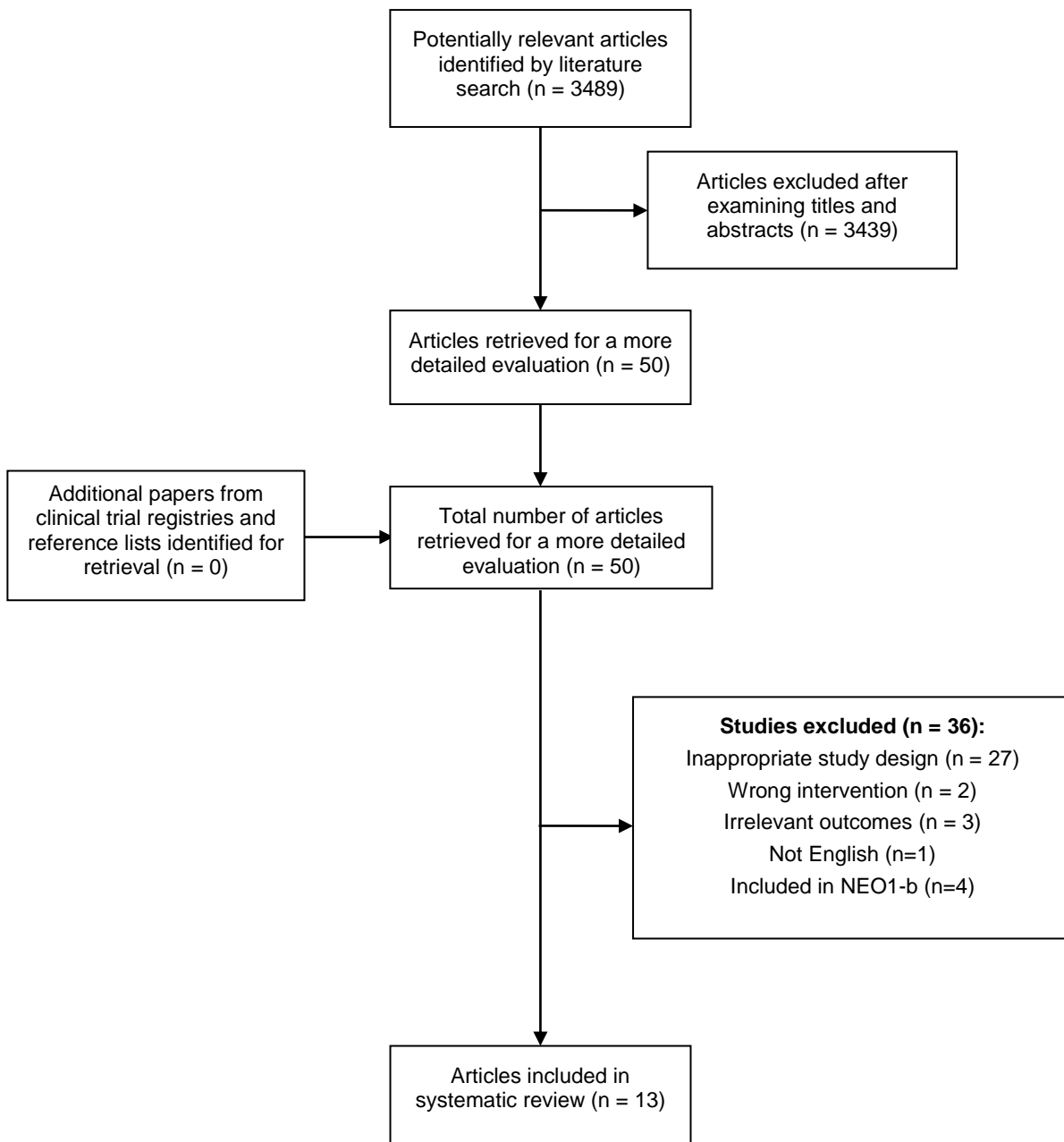
One potentially relevant guideline was identified. However, this was not included as it did not meet the pre-specified criteria. This guideline is detailed in Appendix C.

### 2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The combined PubMed and PsycINFO search identified 958 citations, the Embase search an additional 2466 citations, the CINAHL search an additional 37 citations and the search of the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database identified an additional 28 citations, resulting in a total of 3489 citations. Titles and abstracts were examined and 45 articles were retrieved for a more detailed evaluation. No citations were identified from the reference list of retrieved articles.

In total 11 articles met the specified inclusion criteria. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they had an inappropriate study design (e.g. Avoranta et al., 2011 did not provide an appropriate CRT alone comparison group).



**Figure 1.** Process of inclusion and exclusion of studies

### 2.3. Study Characteristics

Characteristics of included studies are described in Tables 1 - 4.

**Table 1:** Studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Participants	Design	Intervention	Comparator	Outcomes	Comments
<b>Araujo 2015</b> (Brazil)	Rectal cancer patients submitted to neoadjuvant chemotherapy and radiation therapy between September 2002 and December 2013. During this period the standard of care at an institution for locally advanced rectal adenocarcinoma within 10 cm from the anal verge was pre-operative CRT followed by surgical resection <b>Age</b> Median (NOM) = 63.6 years Median (Surgery) = 60.1 years <b>Sex (%)</b> M/F = 51/60  <b>N = 111</b>	Retrospective cohort study	<b>Non-operative management</b> Patients who appeared to have a CCR after neoadjuvant treatment, and who were not submitted to surgery  <b>N = 42</b>	<b>Operative group</b> Operated patients who demonstrated a PCR. All patients received total mesorectal excision and were selected from a database to form a control group  <b>N = 69</b>	<b>Primary</b> Overall survival, disease free survival, relapse-free survival, local relapse, distant relapse, and specific mortality rate	
<b>Dalton 2012</b> (UK)	Tumour and patient characteristics were retrieved from a database of patients undergoing preoperative CRT for rectal cancer with curative intent between 2004 and 2009, with the outcome determined from clinical records. <b>Age</b> Median (CRT) = 64 years Median (Surgery) = 69 years <b>Sex</b> M:F (CRT) = 5:1 M:F (Surgery) = 3.6:1  <b>N = 12</b>	Retrospective cohort study	Patients considered as having a CCR to neoadjuvant CRT  <b>N = 6</b>	Patients undergoing delayed total mesorectal excision due to residual disease following neoadjuvant CRT  <b>N = 6</b>	<b>Reported</b> Disease-free survival	

M=male; F=female; CRT=chemoradiotherapy; CCR=complete clinical response; NOM=non operative management; pCR=pathologically complete response

**Table 2:** Studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Participants	Design	Intervention	Comparator	Outcomes	Comments
<b>Habr-Gama 2004</b> (Brazil)	Two-hundred sixty-five patients with adenocarcinoma of the distal rectum (0–7 cm from anal verge) considered resectable, between 1991 and 2002 at a single institute referred to preoperative CRT. <b>Age</b> Median (Observation) = 58.1 years Median (Surgery) = 53.6 years <b>Sex</b> M:F (Observation) = 1.05 M:F (Surgery) = 1.2  <b>N = 93</b>	Retrospective cohort study	<b>Observation</b> Patients considered as having a CCR to neoadjuvant CRT  <b>N = 71</b>	<b>Surgery</b> Patients with an incomplete clinical response treated by radical surgery following CRT completion  <b>N = 22</b>	<b>Primary</b> Pre-treatment staging, initial tumour size (pre-treatment), distance from anal verge, post-treatment tumour size, overall survival, disease-free survival, and recurrence	Neither group received adjuvant chemotherapy
<b>Lee 2015</b> (Korea)	Rectal cancer patients treated between August 2006 and July 2011 including radiologic complete responders after NCRT without distant metastasis. Rectal cancer was defined as a tumour located ≤15 cm from the anal verge. <b>Age (median, range)</b> Radical surgery = 64 (46-80) years Local excision = 70 (54-82) years Wait-and-see = 70 (50-82) years <b>Sex (M/F)</b> Radical surgery = 21/7 Local excision = 11/5 Wait-and-see = 7/1  <b>N = 52</b>	Retrospective cohort study	<b>Wait-and-see</b> Radiologic complete responders who received CRT without surgery and were closely monitored without routine administration of chemotherapy  <b>N = 8</b>	<b>Local Excision</b> Full thickness excision of the tumour or scar with clear margins was performed <b>N = 16</b>  <b>Radical Surgery</b> All patients underwent standard total mesorectal excision and regional lymphadenectomy <b>N = 28</b>	<b>Primary</b> 3-year disease-free survival, 3-year local recurrence free survival, recurrence <b>Secondary</b> Complications	Most patients who underwent surgery were recommended to receive 5-fluorouracilbased adjuvant chemotherapy regardless of the final pathology.

M=male; F=female; N = number of participants; CRT=chemoradiotherapy; NOM=non operative management; CCR=complete clinical response

**Table 3:** Studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Participants	Design	Intervention	Comparator	Outcomes	Comments
Li 2015 (China)	<p>Patients with resectable (stage II and III) distal rectal adenocarcinoma (0-7 cm from the anal verge) received neoadjuvant CRT at five study centres between April 2006 and October 2013</p> <p><b>Age (median, range)</b> 58 (34-82) years</p> <p><b>Sex (males, %)</b> Observation = 18, 60% Surgery = 60, 65%</p> <p><b>N = 122</b></p>	Prospective cohort study	<p><b>Observation</b> Patients who had a CCR after completing neoadjuvant CRT and were then treated with non-operative management</p> <p><b>N = 30</b></p>	<p><b>Surgery</b> Patients in the surgery group were treated with either APR or LAR with enterostomy</p> <p><b>N = 92</b></p>	<p><b>Primary</b> 5-year disease-free, overall survival, local recurrence and distant metastases</p>	<p>After 3 years if any evidence of recurrence and/or metastasis was detected, salvage treatments, including radical surgery, local excision, radiotherapy with or without chemotherapy, or chemotherapy alone were carried out.</p>
Maas 2011 (Netherlands)	<p>Primary rectal cancer patients aged 18 or older without distant metastases who underwent CRT and showed a clinically complete response or a very good response. Excluded participants with recurrent rectal cancer, distant metastases or refused to comply with the intensive follow-up schedule.</p> <p><b>Age (mean, standard deviation)</b> Observation = 65 (9) years Surgery = 64 (10) years</p> <p><b>Sex (males, %)</b> Observation = 14, 67% Surgery = 16, 18%</p> <p><b>N = 41</b></p>	Prospective cohort study	<p><b>Observation</b> Patients who had a CCR after CRT and did not undergo surgery</p> <p><b>N = 21</b></p>	<p><b>Surgery</b> Patients with a PCR (ypT0N0) after CRT and TME</p> <p><b>N = 20</b></p>	<p><b>Primary</b> Local recurrence</p> <p><b>Secondary</b> Overall survival, disease-free survival, distant metastases-free survival, quality of life, compliance</p>	<p>All patients received adjuvant chemotherapy</p>

*N = number of participants; CRT = chemoradiotherapy; NOM=non operative management; CCR=complete clinical response; pCR=pathologically complete response; TME=total mesorectal excision*

**Table 4:** Studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Participants	Design	Intervention	Comparator	Outcomes	Comments
<b>Renehan 2016</b>  <b>OnCoRe</b>  (UK)	<p>Patients of all ages with a new diagnosis of histologically confirmed rectal adenocarcinoma, without distant metastases, who received preoperative chemoradiotherapy through a single institute between Jan 14, 2011 and April 15, 2013. This study also included all patients managed between March 10, 2005, and Jan 21, 2015, collected through the OnCoRe registry, which obtained data from patients with primary non-metastatic rectal cancers who had received chemoradiotherapy followed by a clinical complete response, and were managed by watch and wait.</p> <p><b>Age (median, range)</b> Observation = 66.9 (60.8-73.2) years Surgery = 65 (57.2-71.6) years</p> <p><b>Sex (males, %)</b> Observation = 97, 76% Surgery = 151, 66%</p> <p><b>N = 357</b></p>	Mixed prospective–retrospective cohort study	<p><b>Observation</b> Received chemoradiotherapy followed by a CCR, and were managed by watch and wait.</p> <p><b>N = 129</b></p>	<p><b>Surgery</b> Patients who had an incomplete clinical response to CRT and were managed by APR, anterior resection, Hartmann’s resection or subtotal colectomy</p> <p><b>N = 228</b></p>	<p><b>Primary</b> Non-regrowth disease-free survival, local pelvic recurrence and distant metastasis</p> <p><b>Secondary</b> Overall survival and colostomy-free survival</p>	
<b>Seshadri 2013</b>  (India)	<p>Patient data extracted from records of 291 rectal cancer patients who received neoadjuvant CRT at a single institution between 1991 and 2008. Patients included those with evidence of T3-4 or node positive disease, or T2 tumours with the intent of sphincter preservation.</p> <p><b>Age (mean, range)</b> Observation = 50 (25-71) years Surgery = 55 (30-69) years</p> <p><b>Sex (males, %)</b> Observation = 14, 61% Surgery = 6, 60%</p> <p><b>N = 33</b></p>	Retrospective cohort study	<p>Patients with a CCR following neoadjuvant CRT</p> <p><b>N = 23</b></p>	<p>Patients without a CCR following neoadjuvant CRT who then proceeded to radical surgery</p> <p><b>N = 10</b></p>	<p><b>Reported outcomes</b> Complications, overall survival, disease-free survival, time to local recurrence</p>	

*N = number of participants; CRT = chemoradiotherapy; NOM=non operative management; CCR=complete clinical response; APR=abdominoperineal resection; OnCoRe=oncological outcomes after clinical complete response in patients with rectal cancer*

**Table 5.1:** Studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Participants	Design	Intervention	Comparator	Outcomes	Comments
<b>Smith 2012</b> (USA)	<p>Patient data extracted from prospective databases, interviews with surgical staff, and the electronic medical records of patients with rectal cancer treated at a single institution from January 2006 to August 2010. Only patients with localized adenocarcinoma of the rectum who received long-course CRT were considered. Patients who presented with distant metastasis were excluded.</p> <p><b>Age (median)</b> Observation = 70 years Surgery = 60 years</p> <p><b>Sex (males, %)</b> Observation = 18, 56% Surgery = 27, 47%</p> <p><b>N = 89</b></p>	Retrospective cohort study	<p><b>Observation</b> Neoadjuvant CRT followed by no operative management after a CCR</p> <p><b>N = 32</b></p>	<p><b>Surgery</b> Patients that received no adjuvant CRT follow by TME with a PCR</p> <p><b>N = 57</b></p>	<p><b>Primary</b> Local recurrence, distant recurrence, disease-free survival, overall survival, time to recurrence</p>	<p>Adjuvant chemotherapy was given to 17 patients in the observation group (54%) and 50 patients (88%) in the operative group</p>
<b>Smith 2015</b> (USA)	<p>Records from 812 patients with rectal adenocarcinoma treated in a single intuition form January 2001 to March 2013. All patients in both the cPR and cCR group underwent long-course neoadjuvant radiotherapy with simultaneous chemotherapy.</p> <p><b>Age (mean)</b> Observation = 62.3 years Surgery = 60.4 years</p> <p><b>Sex (males, %)</b> Observation = 15, 83.3% Surgery = 20, 66.7%</p> <p><b>Ethnicity (Observation Vs. Surgery, %)</b> Asian: 5.6% vs. 6.7% White: 72.2% vs. 80% African American: 11.1% vs. 6.7% Hispanic: 11.1% vs. 3.3% Unknown: 0 vs 3.3%</p> <p><b>N = 47</b></p>	Retrospective cohort study	<p><b>Observation</b> Patients undergoing neoadjuvant CRT with a CCR that opted to undergo surveillance only</p> <p><b>N = 17</b></p>	<p><b>Surgery</b> Patients undergoing APR or LAR with a PCR</p> <p><b>N = 30</b></p>	<p><b>Primary</b> Disease-free survival and overall survival</p>	<p>Eleven of the 18 (61.1 %) patients in the CCR cohort and 18 of the 30 (60 %) patients in the pCR cohort completed a full course of 5-FU-based adjuvant chemotherapy following their course of neoadjuvant therapy and subsequent non-operative or operative management.</p>

*N=number of participants; CRT = chemoradiotherapy; SD=standard deviation; CCR=clinically complete response; pCR=pathologically complete response*

**Table 5.2:** Studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Participants	Design	Intervention	Comparator	Outcomes	Comments
<b>Appelt 2015</b> (Denmark)	<p>Patients were referred from surgical departments throughout Denmark but were treated in a tertiary Danish cancer centre and enrolled in the study before the start of chemoradiotherapy. Eligible patients had primary resectable T2–T3, N0-N1 adenocarcinoma of the rectum within 6 cm of the anal verge. Eligibility criteria included performance status that allowed for long-course treatment with curative intent as well as liver, kidney, and bone marrow function that allowed for long-course chemoradiotherapy, older than 18 years, and no distant metastases.</p> <p><b>Age (median, range)</b> 67 (58-75) years</p> <p><b>Sex</b> Men =39, 76% Female = 12, 24%</p> <p><b>N = 51</b></p>	Prospective cohort study	<p><b>Observation</b> Patients that had a CCR to long-course radiotherapy with concomitant chemotherapy and brachytherapy tumour boost and not receive follow-up surgery</p> <p><b>N = 40</b></p>	<p><b>Follow-up surgery</b> Patients that did not have CCR to neoadjuvant treatment and were treated with APR surgery</p> <p><b>N = 11</b></p>	<p><b>Primary</b> Frequency of local recurrence</p> <p><b>Secondary</b> Frequency of cumulative local recurrence, frequency of distant metastases, overall survival, complications</p>	
<b>Lai 2016</b>	<p>A consecutive series of patients treated at Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China, from 2007 to 2014 for primary rectal cancer. Patients selected for neoadjuvant CRT were required to meet all the following criteria: (a) a biopsy-proven rectal adenocarcinoma, (b) a tumor location up to 10 cm from the anal verge, (c) a primary clinical stage of II–III, and (d) an Eastern Cooperative Oncology Group performance status of 0–2.</p> <p><b>Age (mean, standard deviation)</b> Radical surgery = 63.78 (14.05) years Watch and wait = 67.58 (15.20) years</p> <p><b>Sex (males, %)</b> Radical surgery = 12 (46.15) years Watch and wait = 15 (83.33) years</p> <p><b>N = 54</b></p>	Retrospective cohort study	<p><b>Watch and wait group</b> Patients who had a CCR to CRT and decided to enter in to a watch and wait policy after discussion with surgeon</p> <p><b>N = 18</b></p>	<p><b>Radical surgery group</b> Patients who had a CCR to CRT and decided to have radical resection surgery after discussion with surgeon</p> <p><b>N = 26</b></p>	<p><b>Reported</b> Disease free survival, 5-year overall survival, local recurrence, distant metastases</p>	

*N=number of participants; APR = abdominoperineal resection; CCR=clinically complete response; CRT = chemoradiotherapy; T = tumour; N = node*

## 2.4. Study risk of bias

**Table 6:** Methodological risk of bias of included systematic reviews and meta-analyses (n = 1)

Risk of bias categories	N (%)
Ia. Was an adequate search strategy used?	
2 = Very thorough	0
1 = Adequate	1 (100%)
0 = No, not described	0
Ib. Were the inclusion criteria appropriate and applied in an unbiased way?	
2 = Yes (e.g. pre-specified inclusion criteria applied independently by two people)	1 (100%)
1 = Adequate – pre-specific inclusion criteria applied by one person	0
0 = No – inclusion decided in an arbitrary fashion, not described	0
II. Were the studies assessed for quality?	
2 = Yes (e.g. appropriate assessment, independently by two people)	1 (100%)
1 = Adequate (e.g. problems with quality issues, assessed by one person only)	0
0 = No (e.g. inappropriate, no quality assessment undertaken, not described)	0
III. Were the characteristics and results of individual studies appropriate described?	
2 = Yes (e.g. summary descriptive tables, estimates of treatment effects)	1 (100%)
1 = Adequate (e.g. more information desirable)	0
0 = No	0
IV. Were the methods used for pooling the data appropriate?	
2 = Yes	1 (100%)
0 = No	0
V. If there was heterogeneity, were sources of heterogeneity explored?	
2 = Yes	1 (100%)
1 = Some attempt was made	0
0 = No	0
N/A = No heterogeneity	0

**Table 7:** Methodological risk of bias of included cohort studies (n = 11)

<b>Risk of bias categories</b>	<b>N (%)</b>
la. Selection of subjects in 'new technology' group	11 (91.7%)
2 = Representative of eligible patients	0 (0%)
1 = Selected group	1 (8.3%)
0 = High selected, not described	
lb. Selection of subjects in comparison group	8 (66.7%)
2 = Representative of eligible patients	2 (16.7%)
1 = Selected group	2 (16.7%)
0 = High selected, not described	
II. Comparability of groups on demographic characteristics and clinical features	
2 = Comparable	5 (41.7%)
1 = Not comparable, adjusted analysis used	0 (0%)
0 = Not comparable, not adjusted for differences	7 (58.3%)
IIIa. Were outcome measures blind to technology used?	
2 = Yes	0 (0%)
1 = No, objective measured used	12 (100%)
0 = No, not described	0 (0%)
IIIb. Were the same method of measurement used across comparison groups?	
2 = Yes	10 (83.3%)
0 = No, not described	2 (16.7%)
IV. Were follow-up complete and all patients included in the analysis?	
2 = Yes (e.g. follow-up >95%) or survival analysis using all patients	10 (83.3%)
1 = Reasonable follow-up of all groups (>80%)	1 (8.3%)
0 = No, not described	1 (8.3%)

**Table 8:** Risk of bias assessment summary of included meta-analyses (n=1)

Study	Search strategy	Inclusion criteria	Quality assessment	Appropriate evidence summary	Data pooling methods	Sources of heterogeneity considered	Risk of bias
Li 2016	Adequate	Yes	Yes	Yes	Yes	Yes	Moderate

**Key to overall risk of bias rating**

**Low risk of bias:** A review that received a score of 2 for Questions Ia, Ib, II, and III

**Moderate risk of bias:** A review that received a score of 1 or 2 for Questions Ia, Ib, II, and III

**High risk of bias:** A review that received a score of 0 for any of the Questions Ia, Ib, II, or III

**Table 9:** Risk of bias assessment summary of included cohort studies (n=12)

Article	Subject selection	Comparison group	Comparability	Outcome blinding	Same method between groups	Follow-up completion	Overall risk of bias
Appelt 2015	High	High	High	Moderate	Low	Low	High
Araujo 2015	Low	Low	High	Moderate	Low	Low	High
Dalton 2012	Low	Low	Low	Moderate	Low	Low	Low
Habr-Gama 2004	Low	Low	Low	Moderate	Low	Low	Low
Lai 2016	Low	Low	Low	Moderate	Low	Low	Low
Lee 2015	Low	Low	High	Moderate	Low	Low	High
Li 2015	Low	Low	Low	Moderate	Low	Low	Low
Maas 2011	Low	High	High	Moderate	High	Low	High
Rehnan 2016	Low	Moderate	High	Moderate	High	Low	High
Seshadri 2013	Low	Low	Low	Moderate	Low	Moderate	Moderate
Smith 2012	Low	Moderate	High	Moderate	Low	High	High
Smith 2015	Low	Low	High	Moderate	Low	Low	High

**Key to overall risk of bias rating**

**Low risk of bias:** A study that scored 2 for all risk of bias questions

**Moderate risk of bias:** A study that scored 2 and 1 for all risk of bias questions

**High risk of bias:** A study that scored either 0 for all risk of bias questions, or scored 1 and 0 for all risk of bias questions, or scored 0 for any of the risk of bias questions

## 2.5. Outcomes

**Table 10.** Results of meta-analysis studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	Included studies	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Li 2016	<b>Local recurrence</b> <i>1-year local recurrence rate</i>	Araujo 2015 Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Seshadri 2013 Smith 2015 Li 2015 Lee 2015	585	5.2% (13) N=251	0% N=334	RR=8.18	2.22, 30.07	SSD	1 year
	<b>Local recurrence</b> <i>2-year local recurrence rate</i>	Araujo 2015 Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Seshadri 2013 Smith 2015 Li 2015 Lee 2015	585	8.4% (21) N=251	0.9% (3) N=334	RR=6.96	2.58, 18.80	SSD	2 years
	<b>Local recurrence</b> <i>3-year local recurrence rate</i>	Araujo 2015 Habr-Gama 2004 Seshadri 2013 Smith 2015 Li 2015 Lee 2015	443	10.4% (20) N=192	1.6% (4) N=251	RR=6.97	2.44, 19.93	SSD	3 years
	<b>Local recurrence</b> <i>5-year local recurrence rate</i>	Araujo 2015 Habr-Gama 2004 Seshadri 2013 Smith 2015 Li 2015	407	10% (19) N=184	1.3% (3) N=223	RR=5.69	1.99, 16.25	SSD	5 years

*N=number of participants; RR=risk ratio; SSD=statistically significant difference; NCRT=neoadjuvant chemoradiotherapy*

**Table 11.** Results of meta-analysis studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	Included studies	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Li 2016	<b>Distant metastases</b> <i>1-year distant metastases rate</i>	Araujo 2015 Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Smith 2015 Li 2015 Lee 2015	552	13.2% (3) N=228	0.3% (1) N=324	RR=3.93	0.60, 25.95	NSD	1 year
	<b>Distant metastases</b> <i>2-year distant metastases rate</i>	Araujo 2015 Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Smith 2015 Li 2015 Lee 2015	552	26.3% (6) N=228	3.7% (12) N=324	RR=0.71	0.31, 1.62	NSD	2 years
	<b>Distant metastases</b> <i>3-year distant metastases rate</i>	Araujo 2015 Habr-Gama 2004 Smith 2015 Li 2015 Lee 2015	410	4.7% (8) N=169	5.4% (13) N=241	RR=0.93	0.44, 1.96	NSD	3 years
	<b>Distant metastases</b> <i>5-year distant metastases rate</i>	Araujo 2015 Habr-Gama 2004 Smith 2015 Li 2015	374	6.9% (11) N=161	7.5% (16) N=213	RR=0.95	0.47, 1.91	NSD	5 years

*N=number of participants; RR=risk ratio; NCRT=neoadjuvant chemoradiotherapy; CI=confidence interval; NSD=no significant difference*

**Table 12.** Results of meta-analysis studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	Included studies	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Li 2016	<b>Disease-free survival</b> <i>1-year disease-free survival rate</i>	Araujo 2015 Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Smith 2015 Li 2015 Lee 2015	552	96.1% (219) N=228	99.4% (322) N=324	RR=0.95	0.91, 0.99	NSD	1 year
	<b>Disease-free survival</b> <i>2-year disease-free survival rate</i>	Araujo 2015 Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Smith 2015 Li 2015 Lee 2015	552	92.5% (211) N=228	94.8% (307) N=324	RR=0.97	0.92, 1.03	NSD	2 years
	<b>Disease-free survival</b> <i>3-year disease-free survival rate</i>	Araujo 2015 Habr-Gama 2004 Smith 2015 Li 2015 Lee 2015	410	89.3% (151) N=169	92.9% (224) N=241	RR=0.95	0.85, 1.06	NSD	3 years
	<b>Disease-free survival</b> <i>5-year disease-free survival rate</i>	Araujo 2015 Habr-Gama 2004 Smith 2015 Li 2015	374	88.8% (143) N=161	92.5% (197) N=213	RR=0.96	0.85, 1.08	NSD	5 years

*N=number of participants; RR=risk ratio; NCRT=neoadjuvant chemoradiotherapy; NSD=no significant difference; CI=confidence interval*

**Table 13.** Results of meta-analysis studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	Included studies	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Li 2016	<b>Overall survival</b> <i>1-year overall survival rate</i>	Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Smith 2015 Li 2015	405	100% (178) N=178	99.6% (226) N=227	RR=1.01	0.98, 1.04	NSD	1 year
	<b>Overall survival</b> <i>2-year overall survival rate</i>	Habr-Gama 2004 Maas 2011 Smith 2012 Dalton 2012 Smith 2015 Li 2015	405	99.4% (177) N=178	98.7% (224) N=227	RR=1.02	0.98, 1.06	NSD	2 years
	<b>Overall survival</b> <i>3-year overall survival rate</i>	Habr-Gama 2004 Smith 2015 Li 2015	263	100% (119) N=119	97.9% (141) N=144	RR=1.01	0.97, 1.06	NSD	3 years
	<b>Overall survival</b> <i>5-year overall survival rate</i>	Araujo 2015 Habr-Gama 2004 Smith 2015 Li 2015	374	92.5% (149) N=161	93.4% (199) N=213	RR=1.01	0.92, 1.11	NSD	5 years

*N=number of participants; RR=risk ratio; NCRT=neoadjuvant chemoradiotherapy; NSD=no significant difference; CI=confidence interval*

**Table 14.** Results of studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Araujo 2015 (Brazil)	<b>Local recurrence</b> <i>Rate of isolated local recurrence without distant metastases</i>	111	11% (5) N= 42	1.4% (1) N=69	NR	NR	NR	<b>Observation</b> Median = 44.7 months
	<b>Local recurrence</b> <i>Rate of total local recurrence with and without distant metastases</i>	111	19% (8) N= 42	5.8% (4) N=69	NR	NR	NR	
	<b>Distant metastases</b> <i>Rate of overall distant metastases</i>	111	16.7% (7) N=42	10.1% (7) N=69	<b>RR=1.64</b>	<b>0.62, 4.36</b>	NSD	
	<b>Overall survival</b> <i>Rate of 5-year overall survival</i>	111	71.6% (30) N=42	89.9% N=69	<b>RR=0.79</b>	<b>0.65, 0.98</b>	0.316	
	<b>Disease-free survival</b> <i>5-year disease free survival rate</i>	111	60.9% (26) N= 42	82.8% (57) N=69	<b>RR=0.79</b>	<b>0.65, 0.98</b>	0.011	
	<b>Specific mortality rate</b> <i>5-year specific mortality rate</i>	111	83% N= 42	94% N=69	NR	NR	0.445	5 years
	<b>Overall survival</b> <i>5-year overall survival for tumours ≤ 5cm from anal verge</i>	76	71.7% NR	85.8% NR	NR	NR	0.970	
	<b>Disease free-survival</b> <i>5-year overall survival for tumours ≤ 5cm from anal verge</i>	76	59% (21) NR	75.4% NR	NR	NR	0.081	
Dalton 2012 (UK)	<b>Local recurrence</b> <i>Local recurrence rate</i>	12	0% N=6	0% N=6	NR	NR	NSD	<b>Observation</b> Mean = 25.5 months, range = 12, 45
	<b>Distant metastases</b> <i>Distant metastases rate</i>	12	0% N=6	0% N=6	NR	NR	NSD	
	<b>Overall survival</b> <i>Overall survival rate</i>	12	100% N=6	100% N=6	<b>RR=1.00</b>	<b>0.75, 1.34</b>	NSD	<b>Surgery</b> Mean = 39.3 months, range = 15, 157
	<b>Disease free survival</b> <i>Disease-free survival rate</i>	23	100% N=6	100% N=6	<b>RR=1.00</b>	<b>0.75, 1.34</b>	NSD	

*N=number of participants; RR=risk ratio; NCRT=neoadjuvant chemoradiotherapy; NSD=no significant difference; NR=not reported; CI=confidence interval*

**Table 15.** Results of studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Habr-Gama 2004 (Brazil)	<b>Local recurrence</b> <i>Overall local recurrence rate</i>	93	1.4% (1) N=71	0% N=22	NR	NR	NSD	<b>Observation</b> Mean = 57.3 months, range = 12, 156 <b>Surgery</b> Mean = 48 months, range = 12, 83
	<b>Distant metastasis</b> <i>Overall distant metastasis rate</i>	93	2.8% (2) N=71	13.6% (3) N=22	NR	NR	NSD	
	<b>Disease-free survival</b> <i>5-year disease-free survival rate</i>	93	91.5% (65) N=71	86.4% (190) N=22	<b>RR=1.13</b>	<b>0.95, 1.33</b>	0.090	5 years
	<b>Overall survival</b> <i>5-year overall survival rate</i>	93	100% (71) N=71	90.9% (20) N=22	<b>RR=1.11</b>	<b>0.96, 1.29</b>	0.010	
	<b>Disease-free survival</b> <i>10-year disease-free survival</i>	93	86% N=71	84% N=22	NR	NR	NSD	10 years
	<b>Overall survival</b> <i>10-year overall survival</i>	93	100% N=71	97% N=22	NR	NR	NSD	
Lee 2015 (Korea)	<b>Disease free survival</b> <i>3-year disease free survival rate, observation vs. radical surgery</i>	36	75% (6) N=8	85.7% (24) N=28	<b>RR=0.84</b>	<b>0.55, 1028</b>	0.294	
	<b>Disease free survival</b> <i>3-year disease free survival rate, observation vs. local surgery</i>	24	75% (6) N=8	62.5% (10) N=16	NR	NR	NR	
	<b>Local recurrence</b> <i>3-year local recurrence rate, observation vs. radical surgery</i>	36	25% (2) N=8	3.6% (1) N=28	<b>RR=7.00</b>	<b>0.72, 67.64</b>	0.039	3 years
	<b>Local recurrence</b> <i>3-year local recurrence, observation vs. local surgery</i>	24	25% (2) N=8	31.3% (5) N=16	NR	NR	NR	
	<b>Distant metastases</b> <i>3-year distant metastases rate, observation vs. radical surgery</i>	36	0% N=8	10.7% (3) N=28	<b>RR=0.46</b>	<b>0.03, 8.10</b>	NSD	

N=number of participants; RR=risk ratio; NCRT=neoadjuvant chemoradiotherapy; NSD=no significant difference; NR=not reported; CI=confidence interval

**Table 16.** Results of studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up	
Li 2015 (China)	<b>Overall survival</b>	122	100% (30)	95.6% (88)	<b>RR=1.03</b>	<b>0.97, 1.10</b>	0.262	5 years	
	<i>5-year overall survival rate</i>		N=30	N=92					
	<b>Disease-free survival</b>	122	90% (27)	94.6% (87)	<b>NR</b>	<b>NR</b>	>0.05		
	<i>5-year disease-free survival rate</i>		N=30	N=92					
	<b>Local recurrence</b>	122	6.7% (2)	2.2% (2)	<b>RR=3.07</b>	<b>0.45, 20.84</b>	>0.05		
<i>5-year local recurrence rate</i>	N=30		N=92						
<b>Distant metastases</b>	122	3.3% (1)	5.4% (5)	<b>RR=0.61</b>	<b>0.07, 5.04</b>	>0.05			
<i>5-year distant recurrence rate</i>		N=30	N=92						
Maas 2011 (Netherlands)	<b>Overall survival</b>	41	100% (21)	95% (19)	<b>RR=1.05</b>	<b>0.92, 1.20</b>	NSD	2 years	
	<i>2-year overall survival</i>		N=21	N=20					
	<b>Disease free survival</b>	41	95.2% (19)	95% (19)	<b>RR=0.95</b>	<b>0.80, 1.13</b>	NSD		
	<i>2-year disease free survival rate</i>		N=21	N=20					
	<b>Overall survival probability</b>	41	100%	91%	NR	NR	0.228		
	<i>2-year overall survival probability</i>		N=21	N=20					
	<b>Disease free survival probability</b>	41	89%	93%	NR	NR	0.770		
	<i>2-year disease free survival probability</i>		N=21	N=20					
	<b>Local recurrence</b>	41	4.8% (1)	0%	<b>RR=2.86</b>	<b>0.12, 66.44</b>	NSD		
	<i>Overall local recurrence rate</i>		N=21	N=20					
<b>Distant metastases</b>	41	0%	0%	NR	NR	NSD			
<i>Overall distant metastases rate</i>		N=21	N=20						
<b>Major complications</b>	41	0.5% (1)	35% (7)	NR	NR	NR	Mean = 35, SD = 25 months		
<i>Rate of patients with major post-treatment complications including anastomotic leak, intra-abdominal abscess, and respiratory failure</i>								N=21	N=20
<b>Definitive colostomy</b>	41	NR	45% (9)	NR	NR	NR			
<i>Definitive colostomy rate</i>		N=21	N=20						
<b>Bowel function</b>	41	0.8	3.5	NR	NR	0.182			
<i>Wexner incontinence score, mean</i>		N=21	N=20						
Renehan 2016	<b>Disease-free survival*</b>	218	88.1% (96)	78% (85)	HR=0.50	0.25, 0.98		0.043	
	<i>3-year non-regrowth disease-free survival</i>		N=109	N=109					
OnCoRe	<b>Overall survival*</b>	218	96.3% (105)	87.2% (95)	HR=0.32	0.12, 0.86		0.024	3 years
	<i>3-year overall survival</i>		N=109	N=109					
(UK)	<b>Colostomy free-survival*</b>	218	74% (81)	47% (101)	HR=0.445	0.31, 0.63	<0.001		
	<i>3-year rate of colostomy free survival</i>		N=109	N=109					

N=number of participants; RR=risk ratio; HR=hazard ratio; NCRT=neoadjuvant chemoradiotherapy; NSD=no significant difference; NR=not reported; CI=confidence interval  
\*Propensity score included as a covariate

**Table 17.** Results of studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Seshadri 2013 (India)	<b>Overall survival length</b> <i>Median (range) length of overall survival</i>	33	66 (12-180) months N=23	36 (12-180) months N=10	NR	NR	NR	Observation Median = 72 months
	<b>Disease-free survival length</b> <i>Median (range) length of overall survival</i>	33	36 (5-168) months N=23	37 (18-180) months N=10	NR	NR	NR	
	<b>Local recurrence</b> <i>Rate of overall local recurrence</i>	33	30.4% (7) N=23	0% N=10	RR=6.88	0.43, 109.97	NSD	Surgery Median = 37 months
	<b>Distant metastases</b> <i>Rate of overall distant metastases</i>	33	13% (3) N=23	20% (2) N=10	NR	NR	NR	
	<b>Colostomy free survival</b> <i>Rate of overall colostomy free survival</i>	33	87% (20) N=23	10% (1) N=10	NR	NR	NR	
Smith 2012 (USA)	<b>Overall survival</b> <i>2-year overall survival rate</i>	89	96.9% (31) N=32	100% (57) N=57	RR=0.96	0.89, 1.04	0.560	2 years
	<b>Disease-free survival</b> <i>2-year overall survival rate</i>	89	87.5% (28) N=32	98.2% (56) N=57	RR=0.89	0.89, 1.04	0.270	
	<b>Local recurrence</b> <i>2-year local recurrence rate</i>	89	18.8% (6) N=32	0% N=57	RR=22.85	1.33, 392.84	<0.001	
	<b>Distant metastases</b> <i>2-year local recurrence rate</i>	89	6.3% (2) N=32	1.8% (1) N=57	RR=3.56	0.34, 37.77	0.030	
Smith 2015 (USA)	<b>Overall survival</b> <i>Overall survival rate</i>	48	100% (18) N=18	96.6% (29) N=30	RR=1.02	0.92, 1.14	0.350	Observation Median = 68.4 months
	<b>Disease-free survival</b> <i>Disease-free survival rate</i>	48	88.9% (16) N=18	96.6% (29) N=30	RR=0.92	0.77, 1.10	0.390	
	<b>Local recurrence</b> <i>Local recurrence rate</i>	48	5.6% (1) N=18	0% N=30	RR=4.89	0.21, 114.14	NSD	
	<b>Distant metastases</b> <i>Distant metastases rate</i>	48	5.6% (1) N=18	3.3% (1) N=30	RR=1.64	0.62, 4.36	NSD	Surgery Median = 46.3 months
	<b>Major Complications</b> <i>Rate of major postoperative complications including hemias, anastomotic leak, anastomotic stricture, and rectovaginal fistula</i>	48	0% N=18	56.7% (17) N=30	NR	NR	NR	

N=number of participants; RR=risk ratio; NCRT=neoadjuvant chemoradiotherapy; NSD=no significant difference; NR=not reported; CI=confidence interval

**Table 17.2.** Results of studies comparing rectal cancer surgery with and without neoadjuvant chemoradiotherapy

Study	Outcome	N actual	NCRT + observation	NCRT + surgery	Effect size	CI (95%)	p-value	Follow up
Appelt 2015 (Denmark)	<b>Local recurrence</b> <i>1-year local tumour recurrence rate</i>	51	15.5% N=40	0% N=11	NR	NR	NR	1 year
	<b>Local recurrence</b> <i>2-year local tumour recurrence rate</i>	51	25.9% N=40	0% N=11	NR	NR	NR	2 years
	<b>Distant metastases</b> <i>Overall distant metastases rate</i>	51	7.5% (3) N=40	0% N=11	NR	NR	NR	Median = 26.7 months (IQR = 18.2 to 38)
	<b>Overall survival</b> <i>2-year overall survival</i>	51	100% N=40	100% N=11	NR	NR	NR	2 years
Lai 2016 (Taiwan)	<b>Local recurrence</b> <i>Rate of overall local recurrence</i>	44	11.1% (2) N=18	0% N=26	NR	NR	NR	Mean = 49.92 (watch and wait) 42.28 (radical surgery)
	<b>Distant metastases</b> <i>Rate of overall distant metastases</i>	44	0% N=18	3.8% (1) N=26	NR	NR	NR	
	<b>Disease free-survival</b> <i>Overall disease free survival rate</i>	44	88.8% (16) N=18	95.8% (25) N=26	NR	NR	0.354	
	<b>Overall survival</b> <i>5-year overall survival rate</i>	44	100% (18) N=18	92.3% (24) N=26	NR	NR	0.403	

*N=number of participants; NCRT=neoadjuvant chemoradiotherapy; NR=not reported; CI=confidence interval*

## 2.6 Body of evidence

Effects of interventions on relevant outcomes are described in Tables 17-21.

### I Overall mortality/survival

**Table 18.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on mortality/survival

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*
Li 2016	Meta-analysis of cohort studies	III-2	Moderate	405	<b>1yr overall survival</b> Obs. 100%; Surgery 99.6%	RR=1.01	0.98, 1.04	NSD	1
				405	<b>2yr overall survival</b> Obs. 99.4%; Surgery 98.7%	RR=1.02	0.98, 1.06	NSD	1
				263	<b>3yr overall survival</b> Obs. 100%; Surgery 97.9%	RR=1.01	0.97, 1.06	NSD	1
				374	<b>5yr overall survival</b> Obs. 92.5%; Surgery 93.4%	RR=1.01	0.92, 1.11	NSD	1
				111	<b>5yr overall survival</b> Obs. 71.6%; Surgery 89.9%	RR=0.79	0.65, 0.98	0.316	1
Araujo 2015	Cohort study	III-2	High	76	<b>5yr overall survival ≤ 5cm from AV</b> Obs. 71.7%; Surgery 85.8%	NR	NR	0.970	1
				111	<b>5yr cancer-specific survival</b> Obs. 83%; Surgery 94%	NR	NR	0.445	1
				12	<b>Overall survival</b> Obs. 100%; Surgery 100%	RR=1.00	0.75, 1.34	NSD	1
Dalton 2012	Cohort study	III-2	Low	93	<b>5yr overall survival</b> Obs. 100%; Surgery 97%	RR=1.11	0.96, 1.29	0.010	1
				93	<b>10yr overall survival</b> Obs. 100%; Surgery 97%	NR	NR	NR	1
				122	<b>5yr overall survival</b> Obs. 100%; Surgery 95.7%	RR=1.03	0.97, 1.10	0.262	1
Habr-Gama 2004	Cohort study	III-2	Low	41	<b>2yr overall survival</b> Obs. 100%; Surgery 95%	RR=1.05	0.92, 1.20	NSD	1
				41	<b>2yr overall survival probability</b> Obs. 100%; Surgery 91%	NR	NR	0.228	1
				41	<b>2yr overall survival</b> Obs. 100%; Surgery 100%	NR	NR	NR	1
Li 2015	Cohort study	III-2	Low	51	<b>2yr overall survival</b> Obs. 100%; Surgery 100%	NR	NR	NR	1
				51	<b>2yr overall survival</b> Obs. 100%; Surgery 100%	NR	NR	NR	1
Maas 2011	Cohort study	III-2	High	41	<b>2yr overall survival</b> Obs. 100%; Surgery 95%	RR=1.05	0.92, 1.20	NSD	1
				41	<b>2yr overall survival probability</b> Obs. 100%; Surgery 91%	NR	NR	0.228	1
Appelt 2015	Cohort study	III-2	High	51	<b>2yr overall survival</b> Obs. 100%; Surgery 100%	NR	NR	NR	1
				51	<b>2yr overall survival</b> Obs. 100%; Surgery 100%	NR	NR	NR	1

RR=risk ratio; NSD=no significant difference; NR=not reported; AV=anal verge; CI=confidence interval

**Table 19.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on mortality/survival

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*
<b>Renehan 2016</b>	Cohort study	III-2	High	218	<b>3yr overall survival</b> Obs. 96.3%; Surgery 87.2%	HR=0.32	0.12, 0.86	0.024	1
<b>Seshadri 2013</b>	Cohort study	III-2	Moderate	33	<b>Median overall survival length</b> Obs. 66 mo Surgery 36 mo	NR	NR	NR	1
<b>Smith 2012</b>	Cohort study	III-2	High	89	<b>2yr overall survival</b> Obs. 96.9%; Surgery 100%	RR=0.96	0.89, 1.04	0.560	1
<b>Smith 2015</b>	Cohort study	III-2	High	48	<b>Overall survival</b> Obs. 100%; Surgery 96.6%	RR=1.02	0.92, 1.14	0.350	1
<b>Lai 2016</b>	Cohort study	III-2	Low	44	<b>5yr overall survival</b> Obs. 100%; Surgery 92.3%	NR	NR	0.403	1

*RR=risk ratio; NSD=no significant difference; NR=not reported; HR=hazard ratio; CI=confidence interval*

## II Local recurrence/distant metastases/disease-free survival

**Table 20.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on local recurrence/distant metastases/disease-free survival

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*		
Li 2016	Meta-analysis of cohort studies	III-2	Moderate		<b>1yr local recurrence</b>						
				585	Obs. 5.2%; Surgery 0%	RR=8.18	2.22, 30.07	SSD	1		
					<b>2yr local recurrence</b>						
				585	Obs. 8.4%; Surgery 0.9%	RR=6.96	2.58, 18.80	SSD	1		
					<b>3yr local recurrence</b>						
				443	Obs. 10.4%; Surgery 1.6%	RR=6.97	2.44, 19.93	SSD	1		
					<b>5yr local recurrence</b>						
				407	Obs. 10%; Surgery 1.3%	RR=5.69	1.99, 16.25	SSD	1		
					<b>1yr distant metastases</b>						
				552	Obs. 1.3%; Surgery 0.3%	RR=3.93	0.60, 25.95	NSD	1		
					<b>2yr distant metastases</b>						
				552	Obs. 2.6%; Surgery 3.7%	RR=0.71	0.31, 1.62	NSD	1		
					<b>3yr distant metastases</b>						
				410	Obs. 4.7%; Surgery 5.4%	RR=0.93	0.44, 1.96	NSD	1		
					<b>5yr distant metastases</b>						
				374	Obs. 6.9%; Surgery 7.5%	RR=0.95	0.47, 1.91	NSD	1		
	<b>1yr DFS</b>										
552	Obs. 96.1%; Surgery 99.4%	RR=0.95	0.91, 0.99	NSD	1						
	<b>2yr DFS</b>										
552	Obs. 92.5%; Surgery 94.8%	RR=0.97	0.92, 1.03	NSD	1						
	<b>3yr DFS</b>										
410	Obs. 89.3%; Surgery 92.9%	RR=0.95	0.85, 1.06	NSD	1						
	<b>5yr DFS</b>										
374	Obs. 88.8%; Surgery 92.5%	RR=0.96	0.85, 1.08	NSD	1						

RR=risk ratio; NSD=no significant difference; NR=not reported; DFS=disease-free survival; SSD=statistically significant difference; CI=confidence interval

**Table 21.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on local recurrence/distant metastases/disease-free survival

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*
<b>Appelt 2015</b>	Cohort study	III-2	High	51	<b>1yr local recurrence</b> Obs. 15.5%; Surgery 0%	NR	NR	NR	1
				51	<b>2yr local recurrence</b> Obs. 25.9%; Surgery 0%	NR	NR	NR	1
				51	<b>Overall distant metastases</b> Obs. 7.5%; Surgery 18.2%	NR	NR	NR	1
<b>Araujo 2015</b>	Cohort study	III-2	High	111	<b>Local recurrence without metastases</b> Obs. 11%; Surgery 1.4%	NR	NR	NR	1
				111	<b>Local rec. with/without metastases</b> Obs. 71.7%; Surgery 85.8%	NR	NR	NR	1
				111	<b>Distant metastases</b> Obs.16.7%; Surgery 10.1%	RR=1.64	0.62, 4.36	NSD	1
				111	<b>5yr DFS</b> Obs. 60.9%; Surgery 82.8%	RR=0.79	0.65, 0.98	0.011	1
				76	<b>5yr DFS ≤ 5cm from AV</b> Obs. 59%; Surgery 75.4%	NR	NR	0.081	1
<b>Dalton 2012</b>	Cohort study	III-2	Low	12	<b>Local recurrence</b> Obs. 0%; Surgery 0%	NR	NR	NSD	1
				12	<b>Distant metastases</b> Obs. 0%; Surgery 0%	NR	NR	NSD	1
				12	<b>Overall DFS</b> Obs. 100%; Surgery 100%	RR=1.00	0.75, 1.34	NSD	1
<b>Habr-Gama 2004</b>	Cohort study	III-2	Low	93	<b>Local recurrence</b> Obs.1.4%; Surgery 0%	NR	NR	NSD	1
				93	<b>Distant metastasis</b> Obs. 2.8%; Surgery 13.6%	NR	NR	NSD	1
				93	<b>5yr DFS</b> Obs. 91.5%; Surgery 86.4%	<b>RR=1.13</b>	<b>0.95, 1.33</b>	0.900	1
				93	<b>10yr DFS</b> Obs. 86%; Surgery 84%	NR	NR	NSD	1

RR=risk ratio; NSD=no significant difference; NR=not reported; DFS=disease-free survival; CI=confidence interval

**Table 22.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on local recurrence/distant metastases/disease-free survival

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*
Lee 2015	Cohort study	III-2	High	24	<b>3yr local recurrence</b> Obs. 25%; Local 31.3%	NR	NR	NR	1
				36	<b>3yr local recurrence</b> Obs. 25%; Radical 3.6%	RR=7.00	0.72, 67.64	0.039	1
				36	<b>3yr distant metastases</b> Obs.0 %; Surgery 10.7%	RR=0.46	0.03, 8.10	NSD	1
				24	<b>3yr DFS (obs. vs. local)</b> Obs. 75%; Local 62.5%	NR	NR	NR	1
				36	<b>3yr DFS (obvs. Vs. radical)</b> Obs. 75%; Radical 85.7%	RR=0.84	0.55, 1028	0.294	1
				122	<b>5yr local recurrence</b> Obs. 6.7%; Surgery 2.2%	RR=3.07	0.45, 20.84	>0.050	1
Li 2015	Cohort study	III-2	Low	122	<b>5yr distant metastases</b> Obs. 3.3%; Surgery 5.4%	RR=0.61	0.07, 5.04	>0.050	1
				122	<b>5yr DFS</b> Obs. 90%; Surgery 94.6%	NR	NR	>0.050	1
				41	<b>Local recurrence</b> Obs. 4.8%; Surgery 0%	RR=2.86	0.12, 66.44	NSD	1
Maas 2011	Cohort study	III-2	High	41	<b>Distant metastases</b> Obs. 0%; Surgery 0%	NR	NR	NSD	1
				41	<b>Overall DFS</b> Obs. 95.2%; Surgery 95%	RR=0.95	0.80, 1.13	NSD	1
				41	<b>DFS probability</b> Obs. 89%; Surgery 93%	NR	NR	0.770	1
				218	<b>3yr DFS</b> Obs. 88.1%; Surgery 78%	HR=0.50	0.25, 0.98	0.043	1
Seshadri 2013	Cohort study	III-2	Moderate	33	<b>Local recurrence</b> Obs. 30.4%; Surgery 0%	RR=6.88	0.43, 109.97	NSD	1
				33	<b>Distant metastases</b> Obs. 13%; Surgery 20%	NR	NR	NR	1
				33	<b>DFS length, median</b> Obs. 36mo; Surgery 37mo	NR	NR	NR	1

RR=risk ratio; NSD=no significant difference; NR=not reported; HR=hazard ratio; DFS=disease free survival; CI=confidence interval

**Table 22.2.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on local recurrence/distant metastases/disease-free survival

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*
Smith 2012	Cohort study	III-2	High	89	<b>2yr local recurrence</b>	RR=22.85	1.33, 392.84	<0.001	1
					Obs. 18.8%; Surgery 0%				
					<b>2yr distant metastases</b>				
89	Obs. 6.3%; Surgery 1.8%	RR=3.56	0.34, 37.77	0.030	1				
89	Obs. 87.5%; Surgery 98.2%	RR=0.89	0.89, 1.04	0.270	1				
Smith 2015	Cohort study	III-2	High	48	<b>Local recurrence</b>	RR=4.89	0.21, 114.14	NSD	1
					Obs. 5.6%; Surgery 0%				
					<b>Distant metastases</b>				
48	Obs. 5.6%; Surgery 3.3%	RR=1.64	0.62, 4.36	NSD	1				
48	Obs. 88.9%; Surgery 96.6%	RR=0.92	0.77, 1.10	0.390	1				
Lai 2016	Cohort study	III-2	Low	44	<b>Local recurrence</b>	NR	NR	NR	1
					Obs. 11.1%; Surgery 0%				
					<b>Distant metastases</b>				
44	Obs. 0%; Surgery 3.8%	NR	NR	NR	1				
44	Obs. 88.8%; Surgery 95.8%	NR	NR	0.403	1				

RR=risk ratio; NSD=no significant difference; NR=not reported; HR=hazard ratio; DFS=disease free survival; CI=confidence interval

### III Complications

**Table 23.** Body of evidence examining the effect of the neoadjuvant chemoradiotherapy with and without surgical resection on post-treatment complications

Name of study	Study type	Level of evidence*	Risk of bias	N	Results summary	Size of effect rating	95% CI	p value	Relevance of evidence*
Maas 2011	Cohort study	III-2	High	41	<b>Major complications</b> Obs. 0.5%; Surgery 35%	NR	NR	NR	1
				41	<b>Colostomy free survival</b> Obs. NR; Surgery 45%	NR	NR	NR	1
				41	<b>Wexner incontinence score, mean</b> Obs. 0.8; Surgery 3.5	NR	NR	0.182	1
Renehan 2016	Cohort study	III-2	High	218	<b>3yr colostomy free survival</b> Obs. 74%; Surgery 47%	HR=0.445	0.31, 0.63	<0.001	1
Seshadri 2013	Cohort study	III-2	Moderate	33	<b>Colostomy free survival</b> Obs. 87%; Surgery 10%	NR	NR	NR	1
Smith 2015	Cohort study	III-2	High	48	<b>Major complications</b> Obs. 0%; Surgery 56.7%	NR	NR	NR	1

NR=not reported; HR=hazard ratio; CI=confidence interval

## References: Included studies

1. Appelt, A. L., Ploen, J., Harling, H., Jensen, F. S., Jensen, L. H., Jorgensen, J. C. R., Jakobsen, A. (2015). High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study. *The Lancet Oncology*, 16(8), 919-927.
2. Araujo, R. O. C., et al. (2015), 'Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study', *European Journal of Surgical Oncology*, 41 (11), 1456-63.
3. Dalton, R. S. J., et al. (2012), 'A single-centre experience of chemoradiotherapy for rectal cancer: Is there potential for nonoperative management?', *Colorectal Disease*, 14 (5), 567-71.
4. Habr-Gama, A., et al. (2004), 'Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results', *Ann Surg*, 240 (4), 711-7.
5. Lai, C. L., et al. (2016), 'Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait"', *International Journal of Colorectal Disease*, 31 (2), 413-19.
6. Lee, S. Y., et al. (2015), 'Oncologic outcomes according to the treatment strategy in radiologic complete responders after neoadjuvant chemoradiation for rectal cancer', *Oncology (Switzerland)*, 89 (6), 311-18.
7. Li, J., et al. (2016), 'Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: A systematic review and meta-analysis', *Oncotarget*, 7 (28), 44857-70.
8. Li, J., et al. (2015), 'Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: A cohort study', *Oncotarget*, 6 (39), 42354-61.
9. Maas, M., et al. (2011), 'Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer', *Journal of Clinical Oncology*, 29 (35), 4633-40.
10. Renehan, A. G., et al. (2016), '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 (2), 174-83.
11. Seshadri, R. A., et al. (2013), 'Complete clinical response to neoadjuvant chemoradiation in rectal cancers: can surgery be avoided?' *Hepatogastroenterology*, 60 (123), 410-4.
12. Smith, R. K., et al. (2015), 'Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision', *Int J Colorectal Dis*, 30 (6), 769-74.
13. Smith, J. D., et al. (2012), 'Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy', *Annals of Surgery*, 256 (6), 965-72.

## APPENDICES

### Appendix A: Search strategies used

For PubMed database:

#	Searches
1	rectal neoplasms[mh] OR colorectal surgery[mh]
2	rectal[tiab] OR rectum[tiab] or anus[tiab] or anal[tiab]
3	cancer*[tiab] OR neoplas*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab]
4	2 AND 3
5	1 OR 4
6	neoadjuvant chemorad*[tiab] OR neo-adjuvant chemorad*[tiab] OR preoperative chemorad*[tiab] OR pre-operative chemorad*[tiab] OR definitive chemorad*[tiab] OR total chemorad*[tiab] OR neoadjuvant chemo-rad*[tiab] OR neo-adjuvant chemo-rad*[tiab] OR preoperative chemo-rad*[tiab] OR pre-operative chemo-rad*[tiab] OR definitive chemo-rad*[tiab] OR total chemo-rad*[tiab] OR neoadjuvant radiochemo*[tiab] OR neo-adjuvant radiochemo*[tiab] OR preoperative radiochemo*[tiab] OR pre-operative radiochemo*[tiab] OR definitive radiochemo*[tiab] OR total radiochemo*[tiab] OR neoadjuvant CRT[tiab] OR neo-adjuvant CRT[tiab] OR preoperative CRT[tiab] OR pre-operative CRT[tiab] OR definitive CRT[tiab] OR total CRT[tiab]
7	chemoradiotherapy[mh]
8	6 OR 7
9	5 AND 8
10	English[la]
11	9 AND 10
12	clinical conference[pt] OR comment[pt] OR editorial[pt] OR historical article[pt] OR letter[pt] OR news[pt] OR newspaper article[pt]
13	11 NOT 12
14	2004:3000[dp]
15	13 AND 14

ATSI search terms used in PubMed database:

#	Searches
1	australia[mh] OR Australia*[tiab]
2	ancestry group, oceanic[mh] OR ancestry groups, oceanic[mh] OR aborigine, australian[mh] OR aborigines, australian[mh] OR australian aborigine[mh] OR australian aborigines[mh] OR aborigin*[tiab] OR indigenous[tiab]
3	1 AND 2
4	torres strait islander*[tiab]
5	3 OR 4
6	colorect*[tiab] OR colon*[tiab] OR rectal*[tiab] OR rectum*[tiab] OR anus*[tiab] OR bowel*[tiab]
7	(cancer*[tiab] OR neoplas*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR colorectal neoplasms[mh] OR colonic neoplasms[mh] OR rectal neoplasms[mh])
8	6 AND 7
9	5 AND 8
10	english[la] AND 2004:3000[dp]
11	9 AND 10

For Embase database:

#	Searches
1	rectal tumor/ or rectum cancer/ or rectum carcinoma/ or rectum surgery/
2	((rectal OR rectum OR anus OR anal) adj3 (cancer* OR neoplas* OR oncolog* OR malignan* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)).tw.
3	1 OR 2
4	((chemo-rad* OR chemorad* OR radiochemo* OR CRT) adj1 (definitive OR total OR neoadjuvant OR neo-adjuvant OR preoperative OR pre-operative)).tw.
5	*chemoradiotherapy/
6	4 OR 5
7	3 AND 6
8	(conference OR journal conference abstract OR journal conference paper OR letter OR note).pt.
9	7 NOT 8
10	animal/ NOT human/
11	9 NOT 10
12	limit 11 to yr="2004-current"

ATSI search terms used in Embase database:

#	Searches
1	exp Australia/ OR Australia\$.ti,ab
2	Oceanic ancestry group/ OR aborigin\$.ti,ab. OR indigenous.mp.
3	1 AND 2
4	torres strait\$ islander\$.ti,ab
5	3 OR 4
6	(colorect\$ or colon\$ or rectal\$ or rectum\$ or anus\$ or bowel\$).ti,ab.
7	(cancer\$ or neoplas\$ or oncolog\$ or malignan\$ or tumo?r\$ or carcinoma\$ or adeno).ti,ab.
8	6 AND 7
9	hereditary nonpolyposis colorectal cancer/ or colorectal polyp/ or colorectal tumor/ or colorectal cancer/ or colorectal anastomosis/ or colorectal carcinoma/ or colorectal adenoma/ or colorectal.mp. or hereditary colorectal cancer/
10	colon anastomosis/ or colon carcinoma/ or colon polyposis/ or colon adenocarcinoma/ or colon tumor/ or colon.mp. or colon cancer/ or colon adenoma/ or colon carcinogenesis/ or colon polyp/ or familial colon polyposis/
11	rectum cancer/ or rectum tumor/ or rectum anastomosis/ or rectum carcinoma/ or rectum adenoma/ or rectum/ or rectum polyp/ or rectum.mp.
12	9 OR 10 OR 11
13	8 OR 12
14	5 AND 13
15	limit 14 to english language
16	limit 15 to yr="2004-Current"

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database and PsycINFO:

#	Searches
1	rectal tumor/ or rectum cancer/ or rectum carcinoma/ or rectum surgery/
2	((rectal OR rectum OR anus OR anal) adj3 (cancer* OR neoplas* OR oncolog* OR malignan* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)).tw.
3	1 OR 2
4	((chemo-rad* OR chemorad* OR radiochemo* OR CRT) adj1 (definitive OR total OR neoadjuvant OR neo-adjuvant OR preoperative OR pre-operative)).tw.
5	*chemoradiotherapy/
6	4 OR 5
7	3 AND 6
8	(conference OR journal conference abstract OR journal conference paper OR letter OR note).pt.
9	7 NOT 8
10	animal/ NOT human/
11	9 NOT 10
12	limit 11 to yr="2004-current"

For CINAHL database:

#	Searches
1	Rectal (TX All Text)
2	chemoradiotherapy (TX All Text)
3	1 AND 2
7	2004-3000 (Publication Date)

## Appendix B:

### Level of Evidence rating criteria – Intervention studies

Level	Study type
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: <ul style="list-style-type: none"><li>- Phase II clinical trial</li><li>- Non-randomised, experimental trial</li><li>- Controlled pre-test/post-test study</li><li>- Adjusted indirect comparisons</li><li>- Interrupted time series with a control group</li><li>- Cohort study</li><li>- Case-control study</li></ul> or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"><li>- Phase I clinical trial</li><li>- Historical control study</li><li>- Two or more single arm study</li><li>- Unadjusted indirect comparisons</li><li>- Interrupted time series without a parallel control group</li></ul> or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

*According to the standards of the National Health and Medical Research Council*

## Appendix B continued:

### Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

\*'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)

#### Points for considering patient-relevant outcomes:

- i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
- ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
- iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

Adapted from table 1.10 of: National Health and Medical Research Council. *How to use the evidence: assessment and application of scientific evidence*. Canberra: NHMRC; 2000. [http://www.nhmrc.gov.au/files\\_nhmrc/file/publications/synopses/cp69.pdf](http://www.nhmrc.gov.au/files_nhmrc/file/publications/synopses/cp69.pdf)

## Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title of Guideline	Reason why not adopted
2011	NICE	Colorectal cancer: the diagnosis and management of colorectal cancer	Colon, not rectal cancer. Not enough information to substantiate a systematic review.

### Excluded studies

Study	Reason for Exclusion
Ahn 2012	Inappropriate study design
Akiyoshi 2009	Inappropriate study design
Avoranta 2011	Inappropriate study design
Bergquist 2016	Inappropriate intervention
Brieau 2015	Inappropriate intervention
Buie 2005	Inappropriate study design
Canda 2010	Inappropriate study design
Chawla 2015	Inappropriate study design
Coco 2013	Inappropriate study design
Contin 2014	Inappropriate study design
Denost 2012	Inappropriate study design
Garlipp 2010	Inappropriate study design
Glynn-Jones 2012	Inappropriate study design
Habr-Gama 2014	Inappropriate study design
Hu 2016	Inappropriate study design
Huh 2011	Inappropriate study design
Joye 2016	Inappropriate study design
Kao 2010	Inappropriate study design
Kim 2006	Inappropriate study design
Lykke 2014	No relevant outcomes
Martel 2008	Inappropriate study design
Mozafar 2014	No relevant outcomes
Navarro 2007	Inappropriate study design
Pietsch 2007	No relevant outcomes
Qin 2014	Inappropriate study design
Rezvani 2007	Inappropriate study design
Rosati 2007	Inappropriate study design
Rullier 2008	Inappropriate study design
Shrikhande 2013	Inappropriate study design
Valenti 2007	Inappropriate study design
Williamson 2014	Inappropriate study design

---

Xiong 2009	Not in English
Yeh 2012	Inappropriate study design
Fan 2015	Included in NEO1-b
Park 2011	Included in NEO1-b
Sauer 2012	Included in NEO1-b

---

## References: Excluded Studies

1. Ahn, B. H., et al. (2012), 'Short-term outcomes after laparoscopic surgery following preoperative chemoradiotherapy for rectal cancer', *J Korean Surg Soc*, 83 (5), 281-7.
2. Akiyoshi, T., et al. (2009), 'Safety of laparoscopic total mesorectal excision for low rectal cancer with preoperative chemoradiation therapy', *Journal of Gastrointestinal Surgery*, 13 (3), 521-25.
3. Avoranta, S. T., et al. (2011), 'Securin identifies a subgroup of patients with poor outcome in rectal cancer treated with long-course (chemo)radiotherapy', *Acta Oncologica*, 50 (8), 1158-66.
4. Bergquist, J. R., et al. (2016), 'Is Chemotherapy or Radiation Therapy in Addition to Surgery Beneficial for Locally Advanced Rectal Cancer in the Elderly? A National Cancer Data Base (NCDB) Study', *World J Surg*, 40 (2), 447-55.
5. Brieau, B., et al. (2015), 'Radiochemotherapy versus surgery in nonmetastatic anorectal neuroendocrine carcinoma A multicenter study by the association des gastro-enterologues oncologues', *Medicine (United States)*, 94 (42), e1864.
6. Buie, W. D., et al. (2005), 'Neoadjuvant chemoradiation increases the risk of pelvic sepsis after radical excision of rectal cancer', *Diseases of the Colon and Rectum*, 48 (10), 1868-74.
7. Canda, A. E., et al. (2010), 'Effects of preoperative chemoradiotherapy on anal sphincter functions and quality of life in rectal cancer patients', *International Journal of Colorectal Disease*, 25 (2), 197-204.
8. Chawla, S., et al. (2015), 'Can Surgery be Avoided After Preoperative Chemoradiation for Rectal Cancer in the Era of Organ Preservation? Current Review of Literature', *American journal of clinical oncology*, 38 (5), 534-40.
9. Coco, C., et al. (2013), 'Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer: Short-term morbidity and functional outcome', *Surgical Endoscopy and Other Interventional Techniques*, 27 (8), 2860-67.
10. Contin, P., et al. (2014), 'Comparative analysis of late functional outcome following preoperative radiation therapy or chemoradiotherapy and surgery or surgery alone in rectal cancer', *International Journal of Colorectal Disease*, 29 (2), 165-75.
11. Denost, Q., et al. (2012), 'Laparoscopic surgery for rectal cancer: Preoperative radiochemotherapy versus surgery alone', *Surgical Endoscopy and Other Interventional Techniques*, 26 (7), 1878-83.
12. Fan, W. H., et al. (2015), 'Surgery with versus without preoperative concurrent chemoradiotherapy for mid/low rectal cancer: An interim analysis of a prospective, randomized trial', *Chinese Journal of Cancer*, 34 (9) (no pagination) (25).
13. Garlipp, B., et al. (2010), 'Neoadjuvant chemoradiotherapy for rectal carcinoma: effects on anastomotic leak rate and postoperative bladder dysfunction after non-emergency sphincter-preserving anterior rectal resection. Results of the Quality Assurance in Rectal Cancer Surgery multicenter observational trial', *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie*, 395 (8), 1031-38.
14. Glynne-Jones, R. and Hughes, R. (2012), 'Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation', *British Journal of Surgery*, 99 (7), 897-909.
15. Habr-Gama, A., et al. (2014), '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 (4), 822-28.
16. Hu, M. H., et al. (2016), 'Does neoadjuvant therapy increase the incidence of anastomotic leakage after anterior resection for mid and low rectal cancer? A systematic review and meta-analysis', *Colorectal Dis*.

17. Huh, J. W., et al. (2011), 'Oncologic outcomes of pathologic stage i lower rectal cancer with or without preoperative chemoradiotherapy: Are they comparable?' *Surgery*, 150 (5), 980-84.
18. Joye, I., et al. (2016), 'Survival among clinical stage I-III rectal cancer patients treated with different preoperative treatments: A population-based comparison', *Cancer Epidemiology*, 43, 35-41.
19. Kao, P. S., et al. (2010), 'The impact of preoperative chemoradiotherapy on advanced low rectal cancer', *Journal of Surgical Oncology*, 102 (7), 771-77.
20. Kim, D. W., et al. (2006), 'Pre-operative chemo-radiotherapy improves the sphincter preservation rate in patients with rectal cancer located within 3 cm of the anal verge', *European Journal of Surgical Oncology*, 32 (2), 162-67.
21. Lykke, J., Roikjaer, O., and Jess, P. (2014), 'Tumour stage and preoperative chemoradiotherapy influence the lymph node yield in Stages I-III rectal cancer: Results from a prospective nationwide cohort study', *Colorectal Disease*, 16 (4), O144-O49.
22. Martel, G., et al. (2008), 'Neoadjuvant therapy and anastomotic leak after tumor-specific mesorectal excision for rectal cancer', *Diseases of the Colon and Rectum*, 51 (8), 1195-201.
23. Mozafar, M., et al. (2014), 'Neo-adjuvant chemoradiotherapy; An opportunity in sphincter preserving procedure for rectal cancer', *Gastroenterology and Hepatology from Bed to Bench*, 7 (1), 32-37.
24. Park, J. H., et al. (2011), 'Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer', *Cancer*, 117 (16), 3703-12.
25. Pietsch, A. P., et al. (2007), 'Effect of neoadjuvant chemoradiation on postoperative fecal continence and anal sphincter function in rectal cancer patients', *International Journal of Colorectal Disease*, 22 (11), 1311-17.
26. Qin, C., et al. (2014), 'Does preoperative radio(chemo)therapy increase anastomotic leakage in rectal cancer surgery? A meta-analysis of randomized controlled trials', *Gastroenterology Research and Practice*, 2014 (no pagination) (910956).
27. Rezvani, M., et al. (2007), 'Outcomes in patients treated by laparoscopic resection of rectal carcinoma after neoadjuvant therapy for rectal cancer', *Journal of the Society of Laparoendoscopic Surgeons*, 11 (2), 204-07.
28. Rosati, R., et al. (2007), 'Laparoscopic total mesorectal excision after neoadjuvant chemoradiotherapy', *Surgical Oncology*, 16, 83-89.
29. Rullier, A., et al. (2008), 'Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: Number, status, and impact on survival', *American Journal of Surgical Pathology*, 32 (1), 45-50.
30. Sauer, R., et al. (2012), 'Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years', *Journal of Clinical Oncology*, 30 (16), 1926-33.
31. Shrikhande, S. V., et al. (2013), 'Perioperative outcomes after ultra low anterior resection in the era of neoadjuvant chemoradiotherapy', *Indian Journal of Gastroenterology*, 32 (2), 90-97.
32. Valenti, V., et al. (2007), 'Analysis of early postoperative morbidity among patients with rectal cancer treated with and without neoadjuvant chemoradiotherapy', *Annals of Surgical Oncology*, 14 (5), 1744-51.
33. Valero Navarro, G., et al. (2007), 'Influence of the neo-adjuvant radiochemotherapy as a factor in the surgical treatment of rectal cancer by expert surgeon. A comparative study', *International Journal of Colorectal Disease*, 22 (10), 1233-38.

34. Williamson, J. S., et al. (2014), 'Outcomes in locally advanced rectal cancer with highly selective preoperative chemoradiotherapy', *British Journal of Surgery*, 101 (10), 1290-98.
35. Xiong, H., et al. (2009), 'Application of laparoscopic surgery following neoadjuvant chemoradiotherapy for mid-low rectal cancer. [Chinese]', *Nan fang yi ke da xue xue bao = Journal of Southern Medical University*, 29 (4), 754-56.
36. Yeh, C. H., et al. (2012), 'Comparison of treatment results between surgery alone, preoperative short-course radiotherapy, or long-course concurrent chemoradiotherapy in locally advanced rectal cancer', *International Journal of Clinical Oncology*, 17 (5), 482-90.