NHMRC Evidence Statement Form

Table 1: NHMRC Evidence Statement for clinical question NEO1-a

<table>
<tr><td colspan="2">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?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">Outcome data from 11 level III-2 retrospective and prospective cohort studies were reported in this systematic review. These studies compared patients with a complete clinical response (CCR) to neoadjuvant chemoradiotherapy (NCRT) without follow-up surgery (observation group), to those that did not have a CCR to NRCT and were then treated with local or radical resection (surgery group). Outcomes reported included; overall survival, mortality, disease-free survival, local recurrence, distant metastases, and peri-operative complications including colostomy-free survival and incontinence. A total of six studies had a high risk of bias (Appelt et al., 2015; Araujo et al., 2015; Lee et al., 2015; Maas et al., 2011; Renehan et al., 2016; Smith et al., 2012; Smith et al., 2015), one study had a moderate risk of bias (Seshadri et al., 2013), and four studies had a low risk of bias (Dalton et al., 2012; Habr-Gama et al., 2004; Lai et al., 2016; Li et al., 2015).

Data from one meta-analysis (Li et al., 2015) was also included in this review. This study reported overall survival, local recurrence, distant metastases, and disease-free survival using pooled data from nine cohort studies also included in this systematic review. This meta-analysis had a moderate level of bias.

Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="2">Overall survival
10 cohort studies and one meta-analysis (Li et al., 2016) compared 1, 2, 3 and 5-year survival rates between those patients that had a complete clinical response (CCR) to</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
</table>

NCRT and were not treated with surgery and those patients that received NCRT in addition to surgical tumour resection. Pooled meta-analysis data of six cohort studies (Habr-Gama et al., 2004; Maas et al., 2011; Smith 2012; Dalton et al., 2012; Smith et al., 2015; Li et al., 2015) showed a non-significant difference in 1-year survival across all studies (RR=1.01, 95%CI=0.98-1.04; Li et al., 2016) with high rates of survival observed for non-operative patients. Individual study data also reported no significant differences between groups with the same trend observed. Similarly, meta-analysis data of the same six cohort studies showed non-significant differences for 2-year survival (RR=1.02, 95%CI=0.98-1.06) with individual study data showing the same non-significant effects with non-operative patients having higher rates of 2-year overall survival. 2-year survival was also non-significantly different between groups in Appelt et al., (2015), with 100% overall survival rates observed in both NCRT with watch-and-wait and NCRT with surgery groups. Three-year survival was also found to be non-significantly higher for non-operative patients in a pooled meta-analysis of three studies (RR=1.01, 95%CI=0.97-1.06; Habr-Gama et al., 2004; Smith et al., 2015; Li et al., 2015). One individual study showed a significant difference (Habr-Gama et al. 2004), which reported significantly higher survival rates for patients undergoing NCRT alone compared to those with surgery (RR=1.11, *p*=0.010). Five-year survival was not found to be significantly difference in a pooled analysis of four cohort studies (RR=1.01, 95%CI=0.92-1.11; Araujo et al., 2015; Habr-Gama et al., 2004; Smith et al., 2015; Li et al., 2015). One study not included in this analysis (Renehan et al., 2016) reported significantly higher 5-year survival in patients undergoing NCRT alone compared to those that received surgery (HR=0.32, *p*=0.024). While another study (Lai et al., 2016), showed no significant difference between groups (*p*=0.403). Outside of those studies that found a significant difference between groups (Habr Gama et al., 2004 & Renehan et al., 2016), seven individual studies showed a trend towards higher and longer overall survival in the NCRT alone group. However, these difference were typically very small ranging from 0.4% to 9%.	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

Grade B **Disease-free survival** Ten cohort studies and one meta-analysis (Li et al., 2016) reported 1, 2, 3 and 5-year disease-free survival (DFS) and median DFS length between NCRT groups with and without follow-up surgery. Pooled meta-analysis data of eight cohort studies (Araujo et al., 2015; Habr-Gama et al., 2004; Maas et al., 2011; Smith 2012; Dalton et al., 2012; Smith et al., 2015; Li et al., 2015; Lee et al., 2015) showed a non-significant difference in 1-year DFS across studies (RR=0.95, 95%CI=0.91-0.99; Li et al., 2016) with higher DFS rates in the non-operative group. Individual study data also reported no significant differences between groups. Meta-analysis data of the same eight cohort studies showed non-significant differences for 2-year DFS (RR=0.97, 95%CI=0.92-1.03), with individual studies showing mixed, non-significant difference between groups. Three-year DFS was also found to be non-significantly different in a pooled meta-analysis of five studies with higher DFS rates observed in the non-operation group (RR=0.99, 95%CI=0.85-1.08; Habr-Gama et al., 2004; Araujo et al., 2015; Smith et al., 2015; Li et al., 2015; Lee et al., 2015). Individual studies included in this meta-analysis did not report significant differences for 3-year survival. One other study not included in this meta-analysis, Renehan et al., (2016), showed significantly higher 3-year DFS for the observation group compared to the surgery group (HR=0.50, 95%CI=0.25, 0.98, *p*=0.043). Five-year survival was not found to be significantly difference in a pooled analysis of four cohort studies (RR=0.96, 95%CI=0.77-1.10; Araujo et al., 2015; Habr-Gama et al., 2004; Smith et al., 2015; Li et al., 2015). Only one study (Araujo et al., 2015) included in this meta-analysis observed a significantly lower 5-year DFS rates for non-operative NCRT patients (RR=0.79, 95%CI=0.65-0.98, *p*=0.011). One study not		

included in the meta-analysis also showed no difference between radical resection patients and watch-and-wait patients in terms of 5-year survival (*p*=0.403). Other than Renehan et al., (2016), all cohort studies included in this review observed the non-significantly different DFS rates between groups with differences in DFS rates ranging from 0.2% - 12.5%. **Grade C** **Local recurrence** 10 cohort studies and one meta-analysis compared 1, 2, 3 and 5-year local recurrence rates between NCRT groups with and without follow-up surgery. Pooled meta-analysis data of nine cohort studies (Araujo et al., 2015; Habr-Gama et al., 2004; Maas et al., 2011; Smith 2012; Dalton et al., 2012; Smith et al., 2015; Li et al., 2015; Lee et al., 2015; Seshadri et al., 2012) showed significant differences in 1-year local recurrence across all studies (RR=8.18, 95%CI=2.22-30.07; Li et al., 2016) with lower local recurrence for patients undergoing follow-up surgery. No individual studies included as part of this analysis observed significant differences between groups. In addition to this evidence Appelt et al., (2015) observed lower 1-year local recurrence rates in the NCRT with surgery group (0%) compared to the NCRT with observation group (15.5%), however no statistical comparison was provided. Meta-analysis data of the same nine cohort studies showed significant differences for 2-year local recurrence (RR=6.96, 95%CI=2.58-18.80), with significant differences observed by Smith et al., (2012) who showed lower local recurrence rates in the operative group (RR=22.85, 95%CI=1.33, 392.84). All studies showed equal or lower overall local 2-year recurrence for operative patients. Appelt et al., (2015) also observed lower 2-year local recurrence rates in the NCRT with surgery group (0%) compared to the NCRT with observation group (25.9%). Again, no statistical comparison was provided. Three-year local recurrence rates were also found to be non-significantly different in a pooled meta-analysis of six studies (Habr-Gama et al., 2004; Seshadri et al., 2014;		

Araujo et al., 2015; Smith et al., 2015; Li et al., 2015; Lee et al., 2015) with lower local recurrence rates observed for the operative group (RR=0.99, 95%CI=0.85-1.08; Li et al., 2016). Lee et al., (2015) observed 3-year local recurrence as significantly lower for patients undergoing radical, but not local, resection in comparison to the NCRT observation group (RR=70.00, 95%CI=0.72-67.64, *p*=0.039). Five-year local recurrence was also found to be significantly different in a pooled analysis of five cohort studies (Araujo et al., 2015; Seshadri et al., 2013; Habr-Gama et al., 2004; Smith et al., 2015; Li et al., 2015; RR=0.96, 95%CI=0.77-1.10). One study (Araujo et al., 2015) included in this meta-analysis observed a significantly lower 5-year local recurrence rates for operative patients (RR=13.14, 95%CI=1.70-101.40). The remaining studies showed non-significantly lower local recurrence in the operative group. Overall, other than one study (Araujo et al., 2015) which observed higher local recurrence with and without metastases in the surgery group, all studies observed lower local recurrence rates in the observation group with differences ranging from 4.8% - 30.4%. The largest difference came from a study with a small sample size of 33 participants (Sesahdri et al., 2013), but was not found to be significantly different, (RR=6.88, 95%CI=0.43, 109.97). **Grade B** **Distant metastasis** 10 cohort studies and one meta-analysis (Li et al., 2016) compared 1, 2, 3 and 5-year distant metastases rates between NCRT groups with and without follow-up surgery. Pooled meta-analysis data of eight cohort studies (Araujo et al., 2015; Habr-Gama et al., 2004; Maas et al., 2011; Smith 2012; Dalton et al., 2012; Smith et al., 2015; Li et al., 2015; Lee et al., 2015) showed a non-significant difference in 1-year distant metastases with three local recurrence observed in the non-operative group and one instance observed in operative group (RR=3.93, 95%CI=0.60-25.95). No individual studies included in this meta-analysis observed significant differences between groups for 1-year distant metastases.		

Meta-analysis data of the same eight cohort studies also showed non-significant differences for 2-year local recurrence (RR=0.71, 95%CI=0.31-1.62). For individual cohort studies a significant difference observed only by Smith et al., (2012) which observed lower 2-year distant metastases in the operative group (RR=3.56, 95%CI=0.34-37.77). Three-year distant metastases was also found to be non-significantly different in a pooled meta-analysis of five studies (Habr-Gama et al., 2004; Araujo et al., 2015; Smith et al., 2015; Li et al., 2015; Lee et al., 2015) with slightly lower local recurrence rates observed for the non-operative group (RR=0.95, 95%CI=0.47-1.91; Li et al., 2016). Again, individual studies did not show any significant differences between groups. Similarly, 5-year distant metastases rates was also non-significantly different in a pooled analysis of four cohort studies (Araujo et al., 2015; Habr-Gama et al., 2004; Smith et al., 2015; Li et al., 2015; RR=0.95, 95%CI=0.47-1.91), with individual studies showing no significant differences between groups. In addition to this evidence Appelt et al., (2015) observed higher distant metastases rates in the NCRT with surgery group (18.2%) compared to the NCRT with observation group (7.5%) at a median follow-up of 26.7 months, however no statistical comparison was provided and samples sizes where both small and considerably different in size between groups (n=11 for NCRT+surgery and n = 40 for NCRT+observation) Overall cohort studies revealed mixed results with no significant differences observed between groups for any comparison with four studies showing lower distant metastases for surgery group (2.3-6.6%), four studies showing lower metastases for observation group (2.1–10.8%), and one study showing no difference between groups with both groups having a distant metastases rate of 0%. **Grade C**		

Complications and adverse events Complications and adverse events included major perioperative complications, incontinence and colostomy free survival and were reported across four studies (Mass et al., 2011; Renehan et al., 2016; Seshadri et al., 2013; Smith et al., 2015). Three-year colostomy free survival was significantly higher in the observation group compared to the surgery group (Renehan et al., 2016; HR=0.445, p<0.001). Colostomy-free survival was also higher in the observation group compared to the surgery group (87% vs. 10%) in Seshadri et al., (2013), however statistical comparison was not provided. Observation patients also had fewer major peri-operative complications, however again no statistical comparison of these rates were provided (Maas et al., 2011; Smith et al., 2015). Finally, the Wexner incontinence scales used by Maas et al., (2011), showed a lower mean incontinence score in observation patients compared to surgery patients (0.8 vs. 3.5), however this effect was not statistically significant (*p*=0.182). **Grade C**		
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Overall survival The majority of studies showed slightly higher overall survival rates in rectal cancer patients who had a CCR to NCRT alone compared to those that did not have a CCR and received follow-up surgical resection. Although two significant effects were observed, these effect may be explained by the fact that patients that had a CCR to NRCRT had notably less advanced stage rectal cancer prior to intervention, compared to those that did not have a CCR. As this variables was not included as a covariate in any analysis (in addition to demographic characteristics and distance of the tumour from the anal verge) it is difficult to make definitive conclusions. **Grade D** **Disease-free survival** Comparisons of DFS between groups showed mixed evidence across studies. Only two significant effects where observed with one study showing higher 5-year DFS for patients undergoing NCRT with surgery and another study showing higher 3-year	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

survival for patients that had a CCR to NCRT and did not undergo surgery. Overall, there was no consistent evidence to suggest that DFS varied according to the type of treatment they received. **Grade D** **Local recurrence** Meta-analysis data and data from two cohort studies revealed significantly lower local recurrence rates for patients that received NCRT and surgery compared to those that were not given surgery. The remaining studies observed non-significantly lower local recurrence rates in the observation group. These results suggest that patients had a better response to surgery compared to watchful waiting in relation to rates of local recurrence. **Grade C** **Distant metastasis** There was no good evidence to suggest that rates of distant metastases were different between patients that received NCRT and had a CCR and those patients that received NCRT followed by surgical resection. The results from all nine studies were inconsistent and non-significant. **Grade D** **Complications and adverse events** Although colostomy-free survival was consistently high in patients that did not receive follow-up surgery, this outcome was only examined in three studies of which two had a high risk of bias. Similarly major complications rates, including incontinence as measured by the Wexner incontinence scale, were only reported in two studies which both showed more favourable outcomes in patients that received NCRT alone. However, no statistical comparisons were given for these data. **Grade D**		
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target**

The majority of studies included in this review were conducted in developed countries with one study conducted in India were research was conducted at the Adyar Cancer Institute. All drug regimens and surgical methods used in these trials are commonly used amongst the rectal surgical context in Australia and it is therefore likely that this evidence can be directly generalised to an Australian clinical settings. All patients included across these trials were of either stage I, II or III rectal cancer without distant metastases. The median and mean ages ranged from 50–70 years across studies. Depending on their response to treatment some patients were given adjuvant chemotherapy following their course of NCRT or operative management. **Grade B**		**population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)		
Neoadjuvant chemoradiotherapy with radical resection is a standard treatment option for patients with rectal cancer in Australia and is readily available to most patients. As most of the studies included in this review were conducted on a Western population, the treatment of rectal cancer in these studies may be comparable to the Australian healthcare system in relation to screening and diagnostic procedures. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*		

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	**Rating**	**Description**
1. Evidence base	**D**	Leve III-2 studies with a high risk of bias
2. Consistency	**B** **C** **B** **B** **C**	Overall survival – Grade B Disease-free survival – Grade C Local recurrence – Grade B Distant metastases – Grade B Complications and adverse events – Grade C
3. Clinical impact	**D** **D** **C** **D** **D**	Overall survival – Grade D Disease-free survival – Grade D Local recurrence – Grade C Distant metastases – Grade D Complications and adverse events – Grade D
4. Generalisability	**B**	Evidence directly generalisable to target population with some caveats
5. Applicability	**B**	Evidence applicable to Australian healthcare context with few caveats

Evidence statements:

- Among patients with rectal cancer who have undergone chemoradiation, there is a higher risk of local recurrence with a 'watch and wait' approach compared with patients who have surgery, as evidenced by a meta-analysis observational of cohort studies. However, there was heterogeneity in the design of individual cohort studies.
- Observed disease-free survival rates among patients with rectal cancer did not consistently differ between those who received chemoradiation alone and those who received chemoradiation followed by surgery, despite a higher risk of local recurrence when the 'watch and wait' strategy was used.
- No significant differences in distant metastases or overall survival among patients with rectal cancer were observed between those who received chemoradiation alone and those who received chemoradiation followed by surgery.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** **D**
For patients with rectal cancer who have had a clinical complete response to neoadjuvant chemoradiation, and planned resection according to the standard recommendation is either not possible or the patient declines it, a 'watch and wait' approach can be considered, provided that: • the risks and benefits have been discussed with the multidisciplinary team and the patient • the patient is monitored closely for local recurrence • the patient is offered an appropriate surgical resection procedure if local recurrence is detected.	

PRACTICE POINT (CONSENSUS-BASED RECOMMENDATION)

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation (practice point) can be given.

Practice points:

- A 'watch and wait' approach for patients with clinical complete response following chemoradiation is not considered standard practice. Clinicians and patients who select this option must be aware of increased risk of recurrence necessitating surgical intervention, and the importance of close follow-up.
- Follow-up and surveillance guidelines for a 'watch and wait' approach, in particular the frequency of follow-up tests, are not established. Testing may include serial CEA measurements, clinical examination, radiological surveillance, and sigmoidoscopy/colonoscopy.

Table 2: Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
RCTs have not evaluated chemoradiation alone, compared with neoadjuvant chemoradiation followed by surgery, in patients with rectal cancer. Available evidence is from retrospective or prospective cohort studies in which patients with a clinical complete response underwent a watch-and-wait approach. These observational studies are challenging to interpret, as those patients who have a clinical complete response to chemoradiation may have an improved prognosis, whether or not they subsequently have surgery. There is a higher risk of local recurrence with a watch-and-wait strategy. However, salvage surgery is appropriate and, based on available evidence, appears to achieve similar rates of disease-free survival and overall survival as immediate surgery.

Table 3: Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Choosing observation alone, without surgery, in patients with clinical complete response after chemoradiation is not currently considered standard practice. If observation without surgery is undertaken, the patient needs to understand this is not conventional treatment and compliance with close and strict surveillance is mandatory.	**YES**
Are there any resource implications associated with implementing this recommendation? Strict surveillance would require resourcing for timely clinical review, imaging and examination ideally under anaesthetic. Avoidance of surgery could result in lower costs, but these may be negated by intensive surveillance protocols. Patients who are being followed with 'watch and wait' should ideally be done so with a protocolised regimen of follow-up with prospective data collection.	**YES**

Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Lack of robust evidence may preclude uptake of this strategy. There is concern that patients may not adhere to strict follow up and surveillance, thus potentially rendering a curable early recurrence incurable if detected late. There are definitive recommendations available for optimum follow up strategy in this context.	**YES**