NHMRC Evidence Statement Form

Table 1: NHMRC Evidence Statement for clinical question: REC3:
"What is the most effective treatment for early rectal cancer?**"**

PICO REC3: *In patients diagnosed with stage I-II rectal cancer, what is the most effective treatment strategy to achieve the best outcomes in terms of length and quality of life?*		**Report body of evidence tables**
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)*		
The KCE guideline reported two level III-1 meta-analyses examining the effects of local vs. radical resections on early stage colorectal cancer related outcomes (Kidane et al., 2015; Shaikh et al., 2015). Kidane et al. (2015) included results from twelve level III-2 observational studies and one level II randomised controlled trial, and Shaikh et al. (2015) included six level III-2 observational studies and one level II randomised controlled trial. These studies had a low risk of bias reporting scores of 8 and 9 out of 11 on the AMSTAR risk of bias checklist respectively. Three level II RCTs (Chen et al., 2013; Lezoche et al., 2012; Winde et al., 1996) were also included as part of this review. Only one of these studies reported as assessment of bias (Chen et al., 2013) which was reported as having a high overall risk of bias. The NICE guideline reported five observational studies, however one of these articles was excluded as it compared multiple local resection strategies rather than local vs. radical resection strategies. The four remaining studies that were included in this review met the inclusion criteria of the KCE guideline, and addressed the original clinical question. These studies were all level III-1 evidence (Lee et al., 2003; Lezoche et al., 2014; Palma et al., 2009; Saraste et al., 2013). Two of these studies where reported as having a serious risk of bias (Lee et al., 2003; Lezoche et al., 2014), one had a very serious risk of bias (Saraste et al., 2013), while Plama et al., (2009) reported no serious risk of bias. The update review for both guidelines included one additional meta-analysis of one RCT and 6 observational studies (Lu et al., 2015). This study had a low risk of bias. **Grade C**	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

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)*		
Overall survival Meta analyses included in the KCE guidelines showed the effects of resection type on mortality and survival outcomes. Through analysis of 12 observational studies with a total number of 2,855 participants, Kidane et al., 2015 reported that 5 year overall survival was significantly higher for local resection patients in comparison to radical resection patients (RR=1.46, CI=1.19-1.77, p=0.0002) with RRs ranging from 0.11 to 2.87. When local excision was divided in to TAE and TEMS, a significant effect was not observed for patients undergoing TEMS in comparison to radical resection (RR=1.04, CI=0.69-1.58, p=0.84) but was still significant for TAE (RR=1.75, CI=1.27-2.00, p<0.0001). Shaikh et al., (2015) observed the opposite effect for 4 pooled studies for 10 year overall survival which was non-significantly lower in local versus radical resection patients (OR=0.96, CI=0.38-2.43, p=0.93). As an update to these guidelines, Lu et al., (2015) similarly observed overall survival as non-significantly lower for TEMS patients compared to total mesorectal excision (TME) patients (OR=0.87, CI=0.55-1.38) for T1 patients in 7 pooled observational studies. Observational studies observed mostly small and non-significant differences between patients undergoing local and radical resection surgery. From the RCT studies included in the KCE guidelines Chen et al., (2013) observed 1 year survival as 100% in both TEMS and laparoscopic resection groups. Non-significant differences were also observed by Winde et al., (1996) in which only one patient death was reported in each resection group (TME versus anterior resection, HR=1.02). Observational studies included in the NICE showed similar non-significant differences. In Palma et al., (2009) mortality was non-significantly higher in the TEMs group (17.6%) compared to the TME group (8.8%, RR=1.00, CI=0.07-16.3). In Lee et al., (2003) T1 patients 5 year survival was significantly higher for the TEMS group (100%) compared to the TME group for T1 patients (92.9%, p=0.07), with the opposite non-significant effect observed for T2 patients. In Saraste et al., (2013) overall 5 year survival (all causes) was highest in the anterior resection group (0.8) followed by the abdominoperineal group (0.75), followed by TAE, Hartmann's procedure, endoscopic resection and TAE, however no statistical comparisons were made for this data. As an update to these guidelines, Elmessiry et al., (2014) showed 3 year overall survival as the same for T1 patients in both local excision and TME groups (100%) and non-significantly higher in the TME group (90%) compared to the local excision group (76.9%) for T2 patients. **Grade C**	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

Perioperative mortality Only one study (Kidane et al., 2015) reported in the KCE examined perioperative mortality and observed significantly lower risk in the local resection group when data was examined across two observational studies (RR=0.31, CI=0.14-0.71, p=0.005). **Grade N/A** **Disease free survival** Meta-analysis studies included in the KCE showed mixed effects of resection type on disease free survival. Kidane et al., (2015) observed radical resection group having a significantly higher 5 year disease free survival in comparison to local resection group, (RR=1.54, CI=1.15-2.05, p=0.003). However, this effect may be explained by the increased use of local resection on tumours in the lower third of the rectum, which have poorer prognosis. Shaikh et al., (2015) found that local excision was non-significantly higher in 5 year survival in comparison to the radical resection group, (OR=1.04). As an update to these guidelines, Lu et al., (2015) also observed overall survival as non-significantly higher for TEMS (local) patients compared to TME (radical) (OR=1.12, CI=0.31-4.12, p=0.86). Only one observational study was added to this review (Elmessiry et al., 2014) which found that 3-year disease free survival was non-significantly lower for T1 patients in the local excision group (84.21%) compared to the TME group (94.9%) and significantly lower for T2 patients for the local excision group versus the TME group (61.5% vs. 87.5%). **Grade C** **Local recurrence** The majority of studies indicated higher rates of local recurrence in the local resection group. For meta-analyses included in the KCE. Kidane et al., (2015) observed that local resection was associated with significantly higher rates of local recurrence in comparison to the radical resection group (RR=2.36), and Shaikh et al., (2015) showed non-significantly higher local recurrence in local excision group (10.1%) compared to radical resection (8%, OR=1.29). In addition to this evidence, Lu et al., (2015) found local recurrence was significantly higher for TEMS patients compared to TME patients (OR=4.62, CI=2.03-10.53, p=0.0003). All three RCT studies included in the KCE found non-significantly higher local recurrence in the local excision group. For Chen et al., (2013) local recurrence was higher in TEMS (7.1%) vs. LAR (0%) group, Lezoche et al., (2012) found that cumulative probability of developing recurrence or metastasis at 5 years was 12% in the Endoluminal Loco-Regional		

Resection (ELRR) group and 10% in the TME group, and Winde et al., (1996) observed 4.2% local recurrence in the TME compared to 0% in anterior resection group at 40.9 and 45.8 months median follow-up. Additional evidence from the NICE guidelines reported the same trends in local recurrence rates. Lee et al., (2003) found 5 year local recurrence was non-significantly different between TEMS and TME groups for T1 stage patients (p=0.94), but was significantly higher for the TEMS vs. TME (96.1% vs. 94.7%) for T2 patients (p=0.035). Similarly, Palma et al., (2009) found that local recurrence was non-significantly higher in the TEMs group (5.9%, medium follow-up 86.5 months) compared to the TME group (0%, medium follow-up 93 months), RR=2.57 (CI=0.13-50.7). Finally, one study added to this body of evidence (Elmessiry et al., 2014) found non-significantly higher local recurrence rate in local excision group (18.4%) compared to TME group (5.1%) for T1 stage patients. For T2 patients, local excision had a significantly higher rate of local recurrence (18.4%) compared to the TME group (7.5%). **Grade A** **Distant metastasis** From the KCE guidelines only one meta-analysis *(*Lu et al., 2015) presented data for distant metastasis which reported non-significantly lower for TEMS patients compared to TME patients (OR=0.74, CI=0.32-1.72, p=0.49) across 5 studies with an average follow-up time of 57.2 months which was determined by averaging the median and mean follow-up times presented in these studies. Similarly, all observational studies included in the KCE review failed to find a significant difference between local and radical resection groups; Chen et al., (2013) observed 0% distance metastasis in both TEMS and LAR groups and Winde et al., (1996) found a non-significant difference between TME and anterior resection groups (3.8% vs. 0%) at 40.9 and 45.8 months median follow-up for distant metastasis. Similarly, one article added through consideration of the NICE guidelines (Palma et al., 2009) showed that metastatic recurrence (at a medium follow-up of 86.5 months for local surgery and 93 months for radical surgery) was non-significantly higher in the TEMs group (5.9%) compared to the TME group (RR=2.57, CI=0.13-50.7). **Grade C** **Post-operative complications** Only one meta-analyses and one RCT (both included the KCE guidelines) examined post-operative complications as an outcome, revealing two different outcomes. Kidane et al., (2015) showed that the risk of post-operative complications was significantly lower for the local resection group compared to radical resection group for the total number of all post-op complications (RR=0.16, CI=0.08-0.30) and major post-op complications (RR=0.20,		

CI=0.10-0.41). By contrast, Lezoche et al., (2012) observed an equal percentage of minor and major post-operative complications in both ELRR and TME groups. **Grade D** **Stoma formation** From the KCE guidelines one meta-analysis (Kidane et al., 2015) showed lower stoma formation for local resection compared to radical resection patients (RR=0.17, CI=0.09-0.30). A similar pattern of results was also observed in Lezoche et al., (2012) where patients undergoing endoluminal locoregional resections had significantly fewer temporary and definitive stomas for TEM patients (0% for both temporary and definitive), p<0.001 in comparison to TME patients (11% and 12%, p<0.001). **Grade A** **Quality of life** Only one study (Lezoche et al., 2013) examined quality of life following local versus radical resection. Quality of life was determined by the EORTC QLQ-CR 30. For gastrointestinal problems scores were higher for the TME group at 1, 3 and 6 month follow-up. For global health status scores were higher for TEMS patients at 1 and 3 months and higher for TME at 6 months by 0.4). No statistical comparisons were made for these data. **Grade N/A**		
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 Overall, evidence showed mixed and mostly non-significant differences in survival and mortality rate between local and radical resection patients. KCE guidelines conclude that no evidence regarding the superiority of local versus radical resection for overall survival and that no conclusion could be reached. NICE guidelines state that mortality was low in both groups and that there was no clear difference in mortality between groups, although a clinically important reduction, or increase, in mortality associated with TEMS could not be excluded. Articles included in the update review also did not show higher overall survival for either resection group. **Grade D**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

Disease free survival Similarly, evidence for disease free survival showed negligible differences between local and radical resection groups. KCE guidelines again conclude that there is no evidence regarding the superiority of local vs. radical resection for disease free survival and that no conclusion can be reached. Similarly, articles added to this review also do not show higher disease free survival for either resection group. **Grade D** **Local recurrence** KCE state that there is no good evidence to suggest that local resection does not harm by leading to increased local recurrence or metastases. Similarly, for NICE was no clear difference in recurrence rates between groups across studies with low local recurrence rates in both groups, except for a subgroup with T2 tumours in one observational study which showed higher local recurrence in the TEMS group. Studies added to this review also support the evidence that there is higher local recurrence in local resection patients, especially for those with T2 stage tumours. **Grade D** **Distant metastasis** KCE stated that there is no good evidence that local resection does not harm by leading to increased metastases. Furthermore NICE observed low metastatic recurrence in both groups and describe no clear difference in metastatic recurrence between groups for any study, although a clinically important increase, or decrease, in metastatic recurrence associated with TEMS could not be excluded. Studies added to this review showed lower but comparable distant metastasis in the local excision group. **Grade D** **Post-operative complications** KCE guidelines describe that major post-operative complications are less frequent following local resection as are the number of peri-operative deaths. No evidence was added to this review. **Grade C**		

Stoma and QOL KCE describe the benefits of local resection are less blood loss, a lower number of permanent stoma and shorter hospital stay. NICE describe one observational study assessing the quality of life and bowel function in patients with T1 tumours before and up to 6 months following treatment, however, groups were not statistically compared. **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*		
Studies included in this review are from a wide range of countries including Canada, USA, UK, Germany, Italy, Spain, Sweden and China. Given the majority of these studies were conducted in western countries the evidence may be generalisable to the Australian population where surgical intervention and quality of treatment for rectal cancer may be comparable. When age was reported, the majority of participants where 60-70 years of age. **Grade C**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target 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?)		
The studies included in this review were from a primarily western population where the treatment for early stage rectal cancer may be comparable to the Australian healthcare system. Differences may exist in relation to options available for local and radical resection. **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**	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	**C** **NA** **C** **A** **C** **D** **A** **NA**	Grade C – Overall survival Grade NA - Perioperative mortality Grade C – Disease free survival Grade A – Local recurrence Grade C - Distant metastasis Grade D - Post-operative complications Grade A - Stoma formation Grade NA - Quality of life
3. Clinical impact	**D, D, D, D, C, D**	Grade D – Overall survival Grade D – Disease free survival Grade D – Local recurrence Grade D - Distant metastasis Grade C - Post-operative complications Grade D - Stoma formation and Quality of life
4. Generalisability	**C**	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	**B**	Evidence applicable to Australian healthcare context with few caveats

Evidence statements

There is limited evidence comparing local versus radical excision for early-stage (T1 to T2) rectal cancer in the Australasian population.

Evidence for overall survival showed inconsistent and mostly nonsignificant differences in relation to survival and mortality rates between local and radical resection patients.

There were negligible differences in disease-free survival rates between local and radical resection groups.

Local recurrence rates were higher for patients undergoing local excision, compared with radical resection, particularly among those with T2 stage tumours.

Local recurrence rates did not differ between patients undergoing transanal endoscopic microsurgery and those undergoing transanal local excision.

The rate of distant metastases was similar between local excision and radical resection.

Major postoperative complications and peri-operative mortality were less frequent following local resection than radical excision.

Operative blood loss, permanent stoma rate and hospital stay were all reduced with local excision, compared with radical resection.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** See below

<u>Evidence-based recommendation #1:</u>
For patients with stage 1 rectal cancer (T1/2, N0, M0), cases should be discussed by a multidisciplinary team to determine optimal management with respect to risk of local recurrence, avoidance of a permanent stoma, and fitness for surgery.
Grade C

<u>Evidence-based recommendation #2:</u>
For patients with T1 tumours local excision can be considered, provided that the tumour can be removed with clear margins and that the treating clinician counsels the patient that:

- the risk of local recurrence increases as the T1 tumour stage progresses (from T1sm1 to T1sm2, or from T1sm2 to T1sm3)
- radical resection may be required after histopathological review of the local excision specimen.

Grade D

<u>Evidence-based recommendation #3:</u>
For patients with T2 tumours, consider radical resection as the first option if they are fit for surgery.
Grade C

PRACTICE POINT (CONSENSUS-BASED RECOMMENDATION)

Practice points:

- When determining the optimal management strategy for each patient, the multidisciplinary team, treating clinician and patient should discuss the balance of risks (e.g. local recurrence) and benefits (e.g. avoidance of a permanent stoma), with consideration of the individual's fitness for surgery. The treating clinician should explain to the patient that local excision carries a lower risk of perioperative mortality and a lower permanent stoma rate, but is associated with a higher local recurrence rate, which increases as the depth of tumour invasion increases from T1sm1 to T1sm2 to T1sm3 to T2.

- Radical resection is recommended for patients with T1sm3 tumours, and for those with T2 tumours who are considered fit for radical surgery.

- The use of transanal endoscopic microsurgery or transanal minimally invasive surgery has not shown any significant advantages over transanal local excision, however it is essential to obtain clear resection margins

and the choice of approach to local resection should be determined by the individual surgeon with this factor in mind.

- Application of radiotherapy before or after local excision of rectal cancer may reduce the risk of local recurrence. However, it may have an adverse effect on bowel function.

CONSIDERATIONS

For local excision, the rate of local recurrence increases as the depth of tumour invasion increases from T1sm1 to T1sm2 to T1sm3 to T2. T1sm3 tumours are associated with a significant increase in local recurrence, so this tumour stage may be considered the tipping point for radical resection.

Accurate pathological assessment of the specimen requires that the specimen is removed as a single specimen, regardless of the technique used. Piecemeal resection, whether performed as a surgical resection via local excision, TEMS or TAMIS, or endoscopically through endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR), will result in a compromised specimen with respect to the ability to assess it pathologically.

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.*
The role of neoadjuvant or neoadjuvant radiotherapy, with or without chemotherapy, as an adjunct to local excision of early rectal cancer, remains undetermined. Determination and individualisation of approach also remains uncertain and there is a lack of evidence to make a definitive decision.

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?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
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?	**NO**