Systematic review report for question REC3

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?*

Population	Intervention	Comparator	Outcomes
Patients diagnosed with localised stage I-II potential resectable rectal cancer (nodal status unknown)	Local resection with or without radiotherapy or chemotherapy	Radical resection with or without radiotherapy or chemotherapy	- Overall survival - 30-day survival - Local recurrence (positive nodes or margins) - Rectal cancer mortality - Quality of life - Adverse events - Stoma rates

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials, or Level III-2 comparative studies	
Population	Patients diagnosed with localised stage I-II potential resectable rectal cancer (nodal status unknown)	
Intervention	Local resection with or without radiotherapy or chemotherapy	
Comparator	Radical resection with or without radiotherapy or chemotherapy	
Outcomes	- Overall survival - 30-day survival - Local recurrence (positive nodes or margins) - Rectal cancer mortality - Quality of life - Adverse events - Stoma rates	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

1. Identification of existing relevant guidelines

1.1. Methods

Relevant recent (2005 onwards) guidelines 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).

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/).

2. Results

2.1. Search for relevant guidelines

Two potentially relevant guidelines were identified, these were the Guideline on the management of rectal cancer: update of capita selecta – Part 3: Local vs Radical resection for stage 1 tumours. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE) 2016, and the Addendum to clinical guideline 131: Colorectal cancer: the diagnosis and management of colorectal cancer by National Institute for Health and Care Excellence (NICE), December 2014. Both of these guidelines were subjected to the AGREE II instrument for appraisal. The research question for the KCE guideline was: *Can local resection or transanal endoscopic microsurgical resection be performed instead of radical resection without compromising the outcome in rectal cancer patients (T1, T2)?* The research question for the 2014 NICE guideline was: *What is the most effective treatment for early rectal cancer?* Other guidelines that were identified and reasons for why they were not adopted are described in Appendix C.

2.2. Assessment with AGREE II instrument

The 2016 KCE and 2014 NICE guidelines were independently assessed by three appraisers using the AGREE II instrument. For the KCE guideline the scaled score for the rigour domain was 92.9%, the scaled score for the clarity of presentation domain was 90.5%, and the scaled score for editorial independence was 88.1%. For the NICE guidelines the scaled score for the rigour domain was 91.1%, the scaled score for the clarity of presentation domain was 82.5%, and the scaled score for editorial independence was 90.5%. As such, both guidelines met the inclusion criteria for adoption or adaptation. The authors decided to update the KCE systematic reviews for these questions to 31 August 2016, and adopt or adapt the KCE recommendations for these questions on the basis of results of the updated systematic review. Relevant articles identified in the 2014 NICE guidelines were also included in this review based on the inclusion criteria for the 2016 KCE guideline. However, as not all sections of this report where appropriate for the original research question (as they compared all resection strategies for early rectal cancer, rather than just local vs. radical), only articles reviewed in following sub sections of the 2014 NICE guideline where considered for inclusion:

Transanal endoscopic microsurgery (TEMS) vs radical resection

Chemoradiation and TEMS vs chemoradiation and radical resection

As a result, only one article was identified that was not included in this review (Christoforidis et al., 2009).

2.3 Literature search for updated KCE systematic review

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 rectal cancer. In PubMed, Embase, CINAHL and PsycINFO databases the rectal cancer search was coupled with a search for local and radical resections and database specific filters for identifying randomised controlled trials, controlled clinical trials, systematic reviews and meta-analyses.

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 articles.

Update KCE systematic review – methods and results

KCE question: *Can local resection or transanal endoscopic microsurgical resection be performed instead of radical resection without compromising the outcome in rectal cancer patients (T1, T2)?*

1. Methods

1.1. Literature search to update KCE systematic review

The KCE systematic review search cut-off date was March 2015. To ensure all the relevant literature available was captured, search for the updated systematic review were conducted from 1/1/2014.

1.2. Inclusion criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with stage I (T1-T2) rectal cancer, also after adjuvant therapy	All other stages of rectal cancer
Intervention	Local resection, transanal endoscopic microcsurgery (TEMS)	Any other intervention or comparator or absence of intervention
Comparator	Open or laparoscopic radical surgery	
Outcome	Progression-free survival Metastasis-free survival Local recurrence free survival Overall survival Quality of life	Cost effectiveness
Design	Systematic reviews, meta-analysis, randomised controlled trials and other primary (observational) studies (cohort studies).	Case reports, abstracts, reports with available update
Language	English, French, German, Dutch, Spanish	Other languages
Availability	Full text available	No full text available

2. Results

2.1. Results of KCE guideline literature search update

Figure 1 outlines the process of identifying relevant articles for the systematic review. The combined PubMed and PsycINFO search identified 876 citations, the Embase search an additional 245 citations, the CINAHL search 93 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 369 citations, resulting in a total of 1583 citations. Titles and abstracts were examined and 14 articles were retrieved for a more detailed evaluation.

An additional two potential citations were identified from the reference list of retrieved articles. 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 D. Most articles were excluded because the full details of the study could not be retrieved (e.g. conference abstracts

only). NHMRC levels of evidence and risk of bias of included NICE systematic review studies are documented in Appendix B.

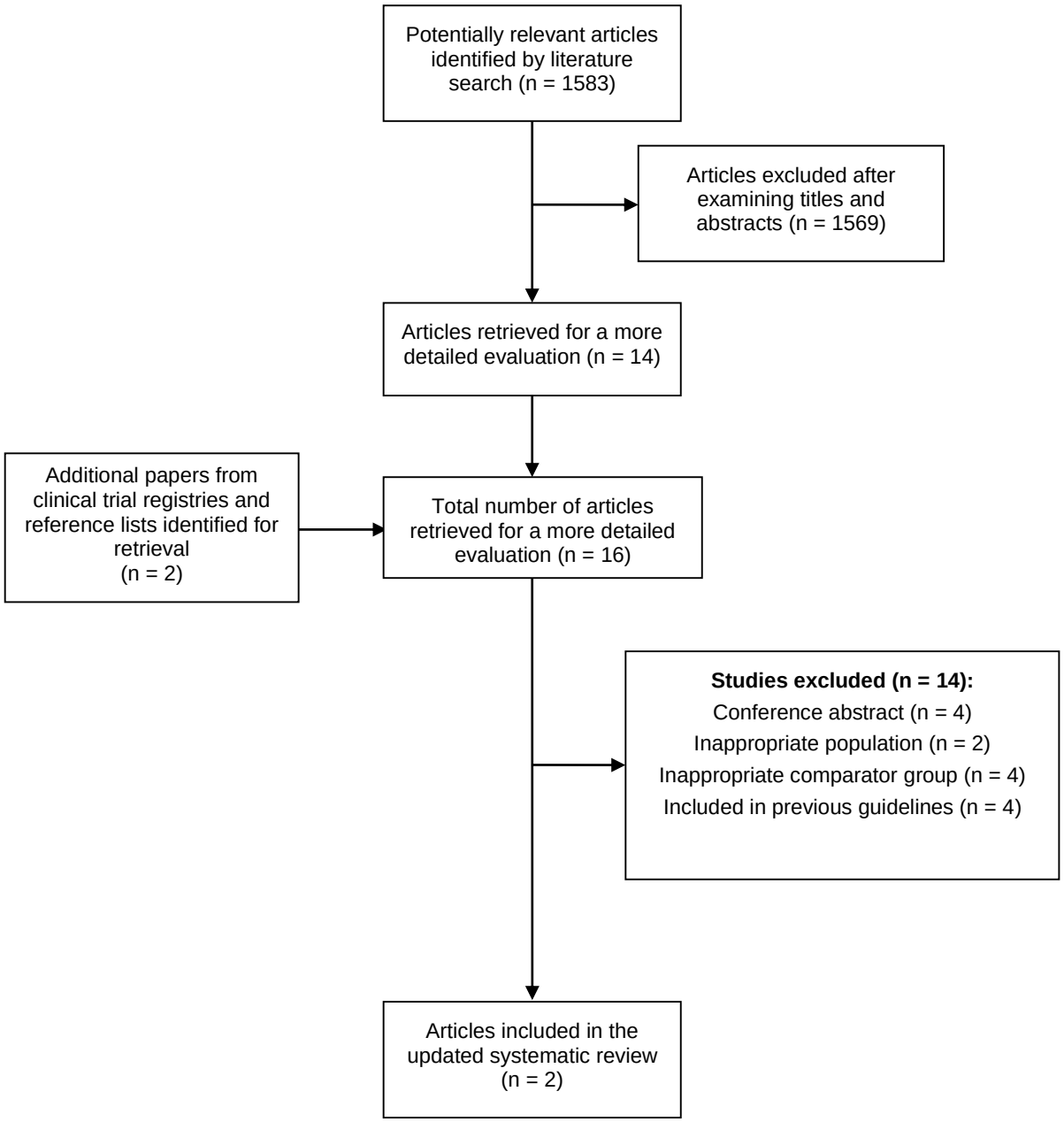

Figure 1. Process of inclusion and exclusion of studies

2.2 Study Characteristics

Characteristics of included studies are described in Table 1

Table 1: Studies examining the relationship between rectal cancer treatment and cancer related outcomes

Study	Participants	Design	Exposure variable	Outcomes	Comments
Elmessiry 2014 (China)	All patients within the American Joint Committee with Cancer Stage I rectal cancer (T1/T2 N0 M0) within 11cm on the anal verge who underwent local excision (LE) or total mesorectal excision (TME) surgery between 2004 and 2012 **LE Age (n = 74):** Mean = 68.7 years SD = 11.9 years **TME Age (n = 79):** Mean = 65.3 ± 15.3 years SD = 15.3 years **Sex:** Male = 70.4% **N = 153**	Retrospective cohort study	LE vs. TME	Local recurrence, 3-year disease-free survival, overall survival	LE compared to TME, no control group.
Lu 2015 (USA)	Patients with a diagnosis of rectal cancer stage T1N0M0 confirmed by pathological examination **N = 860**	Meta-analysis of RCTs and non-randomized CCTs	TEM vs. TME	Local recurrence rate, distant metastasis rate, overall survival, and disease-free survival	

N = number of participants, TEM = Transanal endoscopic microsurgery, TME = total mesorectal excision, RCT = randomised controlled trial, CCT = clinical controlled trial

2.3 Study risk of bias

Table 2: Methodological risk of bias of included case-control studies (n = 1)

Risk of bias categorisation	N (%)
1. Subject selection	
a) Cases	
2 = Representative of eligible patients	-
1 = Selected group	-
0 = Highly selected or not described	1 (100)
b) Adequacy of case definition	
2 = Independent validation of outcome (blind to exposure status)	-
1 = Taken from medical records, self-report without independent validation	1 (100)
0 = Highly selected, inappropriate or not described	-
c) Controls	
2 = From same population as cases and same exclusion criteria used	1 (100)
1 = Selected group (e.g. hospital controls)	-
0 = Highly selected, inappropriate or not described	-
2. Comparability of groups on demographic characteristics and important potential confounders	
2 = Comparable (or matched)	1 (100)
1 = Not comparable but adjusted analysis used	-
0 = Highly selected, inappropriate or not describe	-
3. Ascertainment of exposure/treatment	
2 = Blinded to case/control status	-
0 = No or not described	1 (100)
4. Follow-up complete and all patients included in the analysis?	
2 = Complete response	1 (100)
1 = Non-response unlikely to introduce bias (>80% in both cases and controls)	-
0 = Low response rate (<80%), non-responders not described, differential response in cases/controls, or no details provided	-

Table 3: Methodological risk of bias of systematic reviews and meta-analyses (n = 1)

Risk of bias categories	N (%)
1. **Studies included in the systematic review or meta-analysis**	
a) **Was an adequate search strategy used?**	
2 = Very thorough – included appropriate search terms and databases	1 (100)
1 = Adequate – search terms and/or choice of databases could have been improved upon	-
0 = No or not described	-
b) **Were the inclusion criteria appropriate and applied in an unbiased way?**	
2 = Yes – pre-specified inclusion criteria applied independently by two people	1 (100)
1 = Adequate – inclusion criteria were pre-specified and applied by one person	-
0 = No – inclusion was decided in an arbitrary fashion or not described	-
2. **Were the studies assessed for quality (relating to the minimisation of biases)?**	
2 = Yes – appropriate quality issues were assessed independently by two people	1 (100)
1 = Adequate – some problems with quality issues or assessed by one person only	-
0 = No – inappropriate, no quality assessment undertaken or not described	-
3. **Were the characteristics and results of individual studies appropriately**	
2 = Yes - summary descriptive tables of subjects, intervention, outcomes etc. are provided and estimates of treatment effect displayed	-
1 = Adequate – more information would be desirable	1 (100)
0 = No The following questions are only relevant for systematic reviews that pooled data	-
4. **Were the methods used for pooling the data appropriate?**	
2 = Yes	1 (100)
0 = No)	-
5. If there was heterogeneity, were sources of heterogeneity explored?	
2 = Yes	1 (100)
1 = Some attempt was made	-
0 = No	-
N/A No heterogeneity	-

Table 4: Risk of bias summary assessment of included case-control studies (n = 1)

Article	Cases	Case definition	Controls	Demographic comparability	Exposure	Follow-up	Overall risk of bias
Elmessiry 2014	High	Moderate	Low	Low	High	Low	High risk of bias

Key to overall risk of bias rating
Low risk of bias: A review that received 2 for all risk of bias criteria
Moderate risk of bias: Received 2 and 1 for al risk of bias criteria
High risk of bias: Received 0 for all risk of bias criteria or 1 and 0 for all risk of bias criteria or received 0 for any of the risk of bias criteria

Table 5: Risk of bias summary assessment of included systematic reviews and meta-analyses (n = 1)

Article	Search strategy	Inclusion criteria	Quality assessment	Study charact-eristics	Pooled data	Heterogeneity	Overall risk of bias
Lu 2015	Low	Low	Low	Moderate	Low	Low	Moderate risk of bias

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

2.4 OUTCOMES

Table 6. Results of systematic reviews comparing rectal cancer treatments and cancer related outcomes

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome –primary	Results and other outcomes – secondary	Critical appraisal of review quality
Kidane 2015	• SR and MA • Funding: none • Search date: September 27,2013 • Databases: Medline, Embase, Central, Cinahl, www.clincaltrials.gov, ISI Web of Science, conference proceedings • Study designs: RCT, observational studies: retrospective and prospective cohort • N included studies: N=13 (1 RCT: 53 patients, 12 observational studies: 2802 patients) (Winde,1996; Heintz,1998; Ambacher,1999; Mellgren, 2000; Lee, 2003; Nascimbeni, 2004; Endresth, 2005; Ptok, 2007; You, 2007; Tarantino, 2008; DeGraaf, 2009; Nash, 2009; Palma, 2009)	Eligibility criteria: • Patients with rectal cancer T1N0M0 treated with radical resection or local resection including TAE, TEMS and TAMIS • Patients > 18 yrs	Radical resection vs. local resection including TAE, TEMS and TAMIS.	5 yr OS: LR in comparison with RR 1.46; 95% CI 1.19–1.77, $p = 0.0002$ but 1) no difference in 5-year OS for TEMS vs radical resection 2) meta-regression in case of similar ratio of lower-third cancers: (relative risk, 1.13; 95% CI, 0.93-1.37) ns • All postoperative complications: lower with local resection: pooled RR 0.16 ;95% CI, 0.08–0.30; • Major postoperative complications: lower with local resection: pooled RR 0.20; 95% CI, 0.10 0.41; $p < 0.00001$ • Stoma (QOL): lower with local resection relative risk, 0.17; 95% CI, 0.09–0.30, $p < 0.001$	• 5 yr DFS: Relative risk 1.54; 95% CI 1.15-2.05; $p = 0.003$ • 5 yr DSS: Relative risk 2.00; 95% CI 1.29-3.09; $p = 0.002$ • 5yr local recurrence: increased with local resection: Relative risk 2.36; 95% CI, 1.64–3.39, $p < 0.00001$ • Perioperative mortality lower with local resection: Relative risk, 0.31;95% CI, 0.14–0.71, $p = 0.005$	• Amstar 9/11 items score 'yes' • Pooled observational studies: controversial methodology

SR = systematic review, MA = meta-analysis, N = number of participants, CCT= clinical controlled trial RCT = randomised controlled trial, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, TAMIS = transanal minimally invasive surgery, RR = radical resection, LR = local resection, DFS = disease free survival, OR = odds ratio, CI = confidence interval, OS = overall survival, DSF = disease free survival, DSS = disease specific survival; QOL = quality of life

Table 7. Results of systematic reviews comparing rectal cancer treatments and cancer related outcomes

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome –primary	Results and other outcomes – secondary	Critical appraisal of review quality
Shaikh 2015	• SR and MA Funding: none • Search date: 1946 to July, 2013 • Databases: Medline, Pubmed/Ovid databases and Google Scholar • Study designs: RCT, observational studies: retrospective and prospective cohort • N included studies: N=8 (1 RCT: 100 patients, 7 observational studies: 1301 patients) • (Bannon,1995; Bonnen, 2004; Callender, 2010; Caricato, 2006; HabrGama, 1998; Huh, 2008; Kunderl, 2010; Lezoche, 2012)	Eligibility criteria: • Patients with rectal adenocarcinoma, any stage and post neoadjuvant chemoradiotherapy	Radical resection (RR) vs. local resection (LR) including only studies with direct comparison	10 yr OS (pooled 4 studies): LR in comparison with RR: OR 0.96 ; 95% CI 0.38-2.43, *p* = 0.93 10 yr OS RCT no significant difference Local recurrence (pooled 7 studies): 16/157, 10,1% in LR group vs 95/1144,8% in RR group: OR 1.29, 95% CI 0.72-2,31, p = 0.40; Local recurrence in RCT: 8% in LR 6% in RR group 5yr DFS (pooled 5 studies) OR 1.04, 95% CI 0.61-1.76,p = 0.89 DFS in RCT: no significant difference	• Differences on pre-treatment stage – subgroup analyses for T3: out of scope	• Amstar 9/11 items score 'yes' • Pooled observational studies: controversial methodology
Lu 2015	• SR and MA • Search date: October 2014 • Databases: Cochrane Library, PubMed, Embase and CNKI databases • Study designs: RCT and non-randomised CCT • N included studies: (N = 1 RCT: 50 patients, 7 CCT: 810 patients)	Eligibility criteria • Rectal cancer stage T1N0M0 • Diagnosis confirmed by pathological examination Exclusion criteria • Patients with recurrent rectal cancer	TEMS vs. TME including laparoscopic rectal cancer resection and laparotomic rectal cancer resection	Results from 7 pooled studies • Local recurrence: TEMS vs. TME: OR 4.62, CI 2.03-10.53, *p* = 0.0003 • Distant metastasis: TEMS vs. TME: OR 0.74, CI 0.32-1.72, *p* = 0.49 • Overall survival: TEMS vs. TME: OR 0.87, CI 0.55-1.38, *p* = 0.55 • DFS: TEMS vs. TME: OR 1.12, CI 0.32-4.12, p = 0.86	• Publication biases and meta regression of homogeneity of studies	Moderate risk of bias

SR = systematic review, MA = meta-analysis, N = number of participants, CCT= clinical controlled trial RCT = randomised controlled trial, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, TAMIS = transanal minimally invasive surgery, RR = radical resection, LR = local resection, DFS = disease free survival, OR = odds ratio, CI = confidence interval, OS = overall survival, DSF = disease free survival, DSS = disease specific survival

Table 8. Results from randomised controlled trials comparing rectal cancer treatments and cancer related outcomes

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome (primary)	Results and other outcomes (secondary)	Critical appraisal
Chen 2013	RCT: open but random assignment of treatment	Eligibility criteria: - Rectal cancer staged T1-2N0M0 - According to NCCN guidelines, tumour location 6-15cm proximal to the anal verge, moderately to highly differentiated adenocarcinoma, acceptable physical tolerance Exclusion criteria: Previous surgery **N = 60** Follow up: 5yrs	TEMS (n=28) vs. laparoscopic lower anterior resection (LAR, n=30)	1 yr OS 100% in both groups Local recurrence 7.1% for TEMS vs 0% for LAR (ns) Distant metastases: 0 in both groups Adjuvant Chemotherapy: 3.6% (TEMS) vs 26.7% (LAR) p=0.026 Operative time: 130±.16.7 min vs 198.7±16.8 min p<0.001 Blood loss: 40.7± 13.6ml vs 93.7±39.5 ml p<0.001 Conversion rate, en bloc resection rate, major intraoperative events, blood transfusions: no differences	Pathological outcomes: Clean margins, histological staging and pathological types: no differences	High risk for allocation concealment and differences in adjuvant therapy

N = number of participants, NCCN = National Comprehensive Cancer Network, OS = overall survival, ASA = American Society of Anaesthesiologists, FU = follow up time, RR = radical resection, CI = confidence interval, ELRR = endoluminal locoregional resection, RCT = randomised controlled trial, AR = anterior resection, HR = hazard ratio, LE = local excision, TME = total mesorectal excision, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, LAR = lower anterior resection

Table 9. Results from randomised controlled trials comparing rectal cancer treatments and cancer related outcomes

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome (primary)	Results and other outcomes (secondary)	Critical appraisal
Lezoche 2012 (included in SR by Saikh 2015)	RCT: open but random assignment of treatment	Eligibility criteria: rectal cancer staged T2N0M0 according to NCCN guidelines, repeat staging after adjuvant chemotherapy, fitness *grade I-II* according to American Society of Anaesthesiologists tumour location within 6 cm of the anal verge, moderately (G2) to well (G1) differentiated adenocarcinoma, tumour diameter ≤3cm Exclusion criteria: Higher risk patients ASA II-IV, tumours located > 6cm from the anal verge, poorly (G3) or undifferentiated (G4) tumours, lymphovascular or perineural invasion **N = 100** Minimal follow up: 5 yrs	Endoluminal locoregional resection (ELRR) performed by transanal endoscopic microsurgery (TEM, n=50) vs laparoscopic total mesorectal excision (TME, n=50)	Local recurrence or distant metastases (5 yr FU): 4+2 in ELRR group and 3+2 in TME group, not significant (p=0.686) cumulative probability of developing recurrence or metastasis at 5 yrs (12 % vs 10% but events occurred earlier in ELRR group leading to RR 14.24 (95%CI 1.36-149) p=0.27. Blood loss also had a significant effect on the primary outcome (RR 1.01 95%CI 1.00-1.01 p<0.001)	A significant difference was found for the following secondary outcomes- values given are median with (interquartile range) – always ELRR first, compared with TME 1. Intraoperative programme change: 0(0) vs 6 (12) p=0.013 2. Conversion to open surgery: 0(0) vs 5(10) p=0.028 3. Temporary stoma: 0(0) vs 11(22) p<0.001 4. Definitive stoma: 0(0) vs 12(24) p<0.001 5. Duration of operation (min): 90(90-100) vs 174(160-190) 6. Blood loss (ml) 45(45-45) vs 200 (100-350) p<0.001 7. # patients receiving transfusion: 0(0) vs 10(20) p<0.001 8. # patients receiving analgesia: 7(14) vs 50(100) p<0.001 9. Hospital stay (days): 3(3-4) vs 6(5-7) p<0.001 There was no significant difference in 1. Minor postoperative complications: 6(12) vs 7 (14) p=0.766 2. Major postoperative complications: 1(2) vs 3(6) p=0.25	

N = number of participants, NCCN = National Comprehensive Cancer Network, OS = overall survival, ASA = American Society of Anaesthesiologists, FU = follow up time, RR = radical resection, CI = confidence interval, ELRR = endoluminal locoregional resection, RCT = randomised controlled trial, AR = anterior resection, HR = hazard ratio, LE = local excision, TME = total mesorectal excision, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, LAR = lower anterior resection

Table 10. Results from randomised controlled trial and a non-RCT comparing rectal cancer treatments and cancer related outcomes

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome (primary)	Results and other outcomes (secondary)	Critical appraisal
Winde 1996 (included in SR by Kindane 2015)	RCT: open but random assignment of treatment	Eligibility criteria: Patients with rectal adenocarcinoma GI//II and uT1N negative (staging with intraluminal ultrasound) – Tumours were located within 18 cm of the anal verge. Group A underwent TEM (n=24) had a mean age of 63.7 yrs (range 36-90yrs); M/F ratio 0.7 Group B underwent AR (n=26) had a mean age of 60.9 yrs range 47-81); M/F ratio 1.2 Follow up of a mean of 40.9 mo in TEM group and 45.8 mo in AR group.	TEM n=24 AR=26	Local recurrence: 1/24 in TME group, none in AR group Distant metastases: 1/26 in AR group, none in TME group	1. Operation time: average TEM 103 min vs AR 149 min, p<0.05 2. Blood loss: TEM 143±55 ml vs AR 745±70 ml, p<0.001 3. Hospital stay: TEM 5.7±1.8 days vs AR 15.4±1.5 days, p<0.0001 4. Analgesic (opiates) prescription: TEM average of 5.7 mg/d vs AR 15 mg/d, p<0.0001 5. Early (≤ 30 days) complications: TEM 5/24 vs AR 9/26 6. Late complications: other than local recurrence or distant metastases: TEM 1/24 vs AR 5/26 7. Survival: One patient died in each group HR of dying after TEM was 1.02	
Elmessiry 2014	Non-randomised controlled study	Eligibility criteria: Patients with Cancer Stage I rectal cancer (T1/T2 N0M0) within 11cm on the anal verge who underwent LE or TME surgery between 2004 and 2012 LE = 38 TME = 39		Local recurrence: T1: LE 18.4%, TME 5.1%, p = 0.332 T2: LE 42.3%, TME 7.5%, p = 0.025 Estimated 3-year disease free survival: T1: LE 84.2%, TME 94.9%, p = 0.232 T2: LE 61.5%, TME 87.5%, p = 0.044 Estimated 3 year overall survival: T1: LE 100%, TME 100%, p = ns T2: LE 76.9%, TME 90%, p = 0.351		High risk of bias

N = number of participants, NCCN = National Comprehensive Cancer Network, OS = overall survival, ASA = American Society of Anaesthesiologists, FU = follow up time, RR = radical resection, CI = confidence interval, ELRR = endoluminal locoregional resection, RCT = randomised controlled trial, AR = anterior resection, HR = hazard ratio, LE = local excision, TME = total mesorectal excision, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, LAR = lower anterior resection

Table 11. Relevant observational studies included from NICE 2014 guidelines

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome (primary)	Results and other outcomes (secondary)	Critical appraisal
Lee 2003	Retrospective observational study (review of patient records)	Inclusion criteria: - T1 or T2 cancer with no evidence of lymph node metastasis - 15cm from the anal verge Exclusion criteria: (formulated by reviewer from list of exclusions with reasons) - Preoperative radio or chemotherapy - Positive resection margin - Poorly differentiated or mucinous tumour - Other simultaneous cancer - Follow up loss TEMS group: Sex M/F, (n) 37/37 Age mean (SD) 61.1 (11.2) TME group: Sex M/F, (n) 51/49 Age mean (SD) 57.7 (11.8) **Follow up mean(SD):** TEM: 31 months (17.2) TME: 34.6 months (19.4)	Transanal endoscopic microsurgery (TEMS, full thickness excision including perirectal fat with 1cm resection margin, n = 74) Total mesorectal excision (TME, n =100)	5 year Local recurrence, % T1: TEMS 4.1%, TME 0% p = 0.94 T2: TEMS 19.5% TME 9.4% p = 0.035 5 year survival, % T1: TEMS 100%, TME 92.9% p = 0.07 T2: TEMS 94.7% TME 96.1% p = 0.48	Complication rate, disease free survival	Very low quality of evidence Serious risk of bias

N = number of participants, NCCN = National Comprehensive Cancer Network, OS = overall survival, ASA = American Society of Anaesthesiologists, FU = follow up time, RR = radical resection, CI = confidence interval, ELRR = endoluminal locoregional resection, RCT = randomised controlled trial, AR = anterior resection, HR = hazard ratio, LE = local excision, TME = total mesorectal excision, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, LAR = lower anterior resection

Table 12. Relevant observational studies included from NICE 2014 guidelines

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome (primary)	Results and other outcomes (secondary)	Critical appraisal
Lezoche 2014	Retrospective observational study (using prospective register of data)	Inclusion criteria: - T1 N0 rectal cancer - American Society of Anaesthesiologists grade 1 or 2. Exclusion criteria: - T2 or T3 tumour, lymph node involvement, distant metastasis or local recurrence - Previous anorectal or abdominal surgery - Neoadjuvant or adjuvant radiochemotherapy or ileostomy - Associated pathology that could compromise quality of life - Patients with a stoma TEMS group: Sex M/F (n) 7/10 Age median (range) 67.5 (37-88) TME group: Sex M/F (n) 8/10 Age median (range) 65.8 (39-83) FU: 12 months	Transanal endoscopic microsurgery (TEMS, endoluminal locoregional resection removing mucosa, submucosa, muscolaris propria and adjacent mesorectal fat, n = 20, 3 lost to follow up) Laparoscopic total mesorectal excision (TME, n = 20, 2 lost to follow up)	Quality of life: No statistical analysis presented. (Quality of life was determined by the EORTC QLQ-CR 30. For gastrointestinal problems score were higher for TME at 1, 3 and 6 month follow-up. For global health status scores were higher for TEMS at 1 and 3 months and higher for TME at 6 months by 0.4)		Very low quality of evidence Serious risk of bias

N = number of participants, NCCN = National Comprehensive Cancer Network, OS = overall survival, ASA = American Society of Anaesthesiologists, FU = follow up time, RR = radical resection, CI = confidence interval, ELRR = endoluminal locoregional resection, RCT = randomised controlled trial, AR = anterior resection, HR = hazard ratio, LE = local excision, TME = total mesorectal excision, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, LAR = lower anterior resection

Table 13. Relevant observational studies included from NICE 2014 guidelines

Reference	Methodology	Patient characteristics	Intervention(s)	Results outcome (primary)	Results and other outcomes (secondary)	Critical appraisal
Palma 2009	Retrospective observational study (of prospectively collected database)	Inclusion criteria: - T1 N0 rectal cancer - Well or moderately well-differentiated Exclusion criteria: - Lymphovascular or neuronal invasion TEMS group: Sex not specified Age mean (sd) 68.4 (10.7) Radical surgery group: Sex not specified Age mean (sd) 65.6 (9.7) FU: TEMS: Median 86.5 months (range 48-113) Radical surgery: 93.0 months (range 48-108)	Transanal endoscopic microsurgery (TEMS, full wall thickness excision with attempted margin of 1cm) (n = 34) Radical surgery (Total mesorectal excision, anterior resection or Hartmann procedure, n = 17)	Local recurrence at any time in follow up period: TEMS n = 2/34, radical n = 0/34, p = 0.55, relative risk = 2.57 (0.13-50.7) Metastatic recurrence at any time in follow up period: TEMS n = 2/34, radical n = 0/34, p = 0.55, relative risk = 2.57 (0.13-50.7) Mortality at any time in follow up period: TEMS n = 6/34, radical n = 3/34, p = 0.673, relative risk = 1.00 (0.07-16.3)	Operating time, blood loss, time of hospitalisation, complication rate	Very low quality of evidence No serious risk of bias
Saraste 2013	Retrospective observational study (using prospective register of data)	Inclusion criteria: - T1-T2 N0 M0 rectal cancer Exclusion criteria: - All patients treated for stage I rectal cancer were included in the overall analysis. Only local excision by endoscopic resection, transanal excision or transanal endoscopic microsurgery are reported here. Baseline characteristics: Not reported separately for each group FU: 5 years	Transanal endoscopic microsurgery (TEMS, n = 98) Endoscopic resection (ER, n = 55), Transanal excision (TAE, n =210) Anterior resection (AR, n = 1947) Abdominoperineal resection (APR, n =982) Hartmann's procedure (HP, n =253)	Overall 5 year survival (all causes, cumulative probability, 95% CI) AR: 0.8 (0.78-0.82) APR: 0.75 (0.72-0.77) HP: 0.57 (0.50-0.63) ER: 0.57 (0.44-0.71) TAE: 0.61 (0.54-0.68) TEMS: 0.56 (0.46-0.66) Relative 5 year survival (mortality due to diseases, cumulative probability, 95% CI) AR: 0.95 (0.92-0.97) APR: 0.89 (0.85-0.93) HP: 0.77 (0.69-0.87) ER: 0.76 (0.76-0.94) TAE: 0.82 (0.73-0.91) TEMS: 0.75 (0.62-0.88)	Multivariate analysis of risk factors affecting survival, subgroup analysis by age	Very low quality Very serious risk of bias

N = number of participants, SD = standard deviation, CI = confidence interval, RCT = randomised controlled trial, AR = anterior resection, HR = hazard ratio, LE = local excision, TME = total mesorectal excision, TAE = transanal excision, TEMS = transanal endoscopic microsurgery, LAR = lower anterior resection, EORTC QLQ = The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

References: Included studies

KCE/NICE update Review

1. Elmessiry MM, Van Koughnett JA, Maya A, DaSilva G, Wexner SD, Bejarano P, et al. Local excision of T1 and T2 rectal cancer: proceed with caution. Colorectal Dis. 2014;16(9):703-9.

2. Lu JY, Lin GL, Qiu HZ, Xiao Y, Wu B, Zhou JL. Comparison of Transanal Endoscopic Microsurgery and Total Mesorectal Excision in the Treatment of T1 Rectal Cancer: A Meta-Analysis. PLoS One. 2015;10(10):e0141427.

KCE Guideline

1. Kidane B, Chadi SA, Kanters S, Colquhoun PH, Ott MC. Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. Dis Colon Rectum. 2015;58(1):122-40

2. Shaikh I, Askari A, Ouru S, Warusavitarne J, Athanasiou T, Faiz O. Oncological outcomes of local excision compared with radical surgery after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis. 2015;30(1):19-29.

3. Chen YY, Liu ZH, Zhu K, Shi PD, Yin L. Transanal endoscopic microsurgery versus laparoscopic lower anterior resection for the treatment of T1-2 rectal cancers. Hepatogastroenterology. 2013;60(124):727-32.

4. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg. 2012;99(9):1211-8.

5. Winde G, Nottberg H, Keller R, Schmid KW, Bunte H. Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection. Dis Colon Rectum. 1996;39(9):969-76.

NICE Guideline (which met the KCE inclusion criteria)

1. Lee W, Lee D, Choi S et al. Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer: Retrospective study. Surgical Endoscopy and Other Interventional Techniques. 2003;17: 1283-7.

2. Lezoche E, Paganini AM, Fabiani B et al. Quality-of-life impairment after endoluminal locoregional resection and laparoscopic total mesorectal excision. Surgical Endoscopy and Other Interventional Techniques 2014;28: 227-34.

3. Palma P, Horisberger K, Joos A et al. Local excision of early rectal cancer: is transanal endoscopic microsurgery an alternative to radical surgery? Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva. 2009;101: 172-8.

4. Saraste D, Gunnarsson U, Janson M. Local excision in early rectal cancer-outcome worse than expected: a population based study. European Journal of Surgical Oncology: the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2013;39: 634-9.

APPENDICES

Appendix A: Search strategies used

For PubMed database:

#	Searches
1	colorectal tumor[MeSH Terms]
2	(colorect*[tiab] OR rectal*[tiab] OR rectum*[tiab] OR bowel*[tiab]) AND (cancer*[tiab] OR neoplas*[tiab] or oncolog*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab])
3	1 OR 2
4	(transanal*[tiab] OR trans-anal*[tiab]) AND (microsurg[tiab] OR operation[tiab] OR resection*[tiab])
5	TEMS[tiab] OR TEM[tiab] OR TEO[tiab]
6	endoscop*[tiab] AND (mucosal*[tiab] OR submucosal*[tiab])
7	brachytherapy[MeSH Terms]
8	brachytherap*[tiab]
9	papillon*[tiab]
10	(therap*[tiab] OR radiotherap*[tiab] OR radioisotope*[tiab] OR radiation[tiab]) AND (interstitial[tiab] OR plaque[tiab] OR implant[tiab] OR surface[tiab] OR intracavit*[tiab] OR contact[tiab])
11	curietherap*[tiab] OR endocurietherap*[tiab]
12	(bowel*[tiab] OR abdominoperineal[tiab] OR anorectal[tiab] OR anterior[tiab] OR anteroposterior[tiab] OR local OR radical) AND (excision*[tiab] OR remov*[tiab] OR resection*[tiab])
13	glove*[tiab] AND port*[tiab]
14	single incision laparoscopic surg*[tiab] OR SILS[tiab]
15	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16	3 AND 15
17	meta-analysis[pt]
18	meta-analysis as topic[MeSH Terms]
19	review[pt]
20	review literature as topic[MeSH Terms]
21	metaanaly*[tiab] OR metanaly*[tiab] OR metaanalysis[tiab] OR metaanalyses[tiab]
22	review*[ti] OR overview*[ti]
23	systematic[tiab] AND (review[tiab] OR overview[tiab])
24	(quantitative$[tiab] OR qualitative$[tiab]) AND (review$[ti] OR overview$[ti])
25	(studies[tiab] OR trial*[tiab]) AND (review$[tiab] OR overview$[tiab])
26	(integrat*[tiab] AND (research[tiab] OR review$[tiab] OR literature[tiab])
27	pool*[tiab] AND (analys*[tiab] OR data[tiab])
28	handsearch[tiab] OR handsearched[tiab]
29	manual search[tiab] OR manually searched[tiab]
30	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31	Randomized Controlled Trial[pt]
32	Controlled Clinical Trial[pt]
33	Clinical Trial[pt]
34	Clinical Trials as Topic[MeSH Terms]
35	Placebos[MeSH Terms]
36	Random Allocation[MeSH Terms]
37	Double-Blind Method[MeSH Terms]
38	Single-Blind Method[MeSH Terms]
39	Cross-Over Studies[MeSH Terms]
40	(random$[tiab] OR control$[tiab] OR clinical$[tiab]) AND (trial$[tiab] OR stud$[tiab])
41	random*[tiab] AND allocate*[tiab]
42	placebo$[tiab]

43	(singl*[tiab] or doubl*[tiab] or trebl*[tiab] or tripl*[tiab]) AND (blind*[tiab] or mask*[tiab])
44	crossover*[tiab] OR cross over[tiab]
45	31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44
46	30 OR 45
47	16 AND 46
48	(English[la])
49	(2014:3000[dp])
50	47 AND 48 AND 49

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 2014:3000[dp]
11	9 AND 10

For Embase database:

#	**Searches**
1	exp colorectal tumor/
2	((colorect* or rectal* or rectum* or bowel*) adj4 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma*)).tw.
3	or/1-2
4	((Transanal* or trans-anal*) adj4 (microsurg* or operation or resection*)).tw.
5	(TEMS or TEM or TEO).tw.
6	(Endoscop* adj4 (mucosal* or submucosal*)).tw.
7	brachytherapy/
8	brachytherap*.tw.
9	papillon*.tw.
10	((therap* or radiotherap* or radioisotope* or radiation) adj4 (interstitial or plaque or implant or surface or intracavit* or contact)).tw.
11	(curietherap* or endocurietherap*).tw.
12	((bowel* or abdominoperineal or anorectal or anterior or anteroposterior or local or radical) adj4 (excision* or remov* or resection*)).tw.
13	(glove* adj4 port*).tw.
14	((single adj1 incision adj1 laparoscopic adj1 surg*) or SILS).tw.
15	or/4-14

16	3 and 15
17	animal/ not human/
18	16 not 17
19	limit 18 to english language
20	Meta-Analysis/
21	Meta-Analysis as Topic/
22	Review.pt.
23	exp Review Literature as Topic/
24	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
25	(review$ or overview$).ti.
26	(systematic$ adj5 (review$ or overview$)).tw.
27	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
28	((studies or trial$) adj2 (review$ or overview$)).tw.
29	(integrat$ adj3 (research or review$ or literature)).tw.
30	(pool$ adj2 (analy$ or data)).tw.
31	(handsearch$ or (hand adj3 search$)).tw.
32	(manual$ adj3 search$).tw.
33	or/20-32
34	animal/ not human/
35	33 not 34
36	Randomized Controlled Trial/
37	Controlled Clinical Trial/
38	Clinical Trial/
39	exp Clinical Trials as Topic/
40	placebo/
41	randomization/
42	double blind procedure/
43	Single-blind Method/
44	crossover procedure/
45	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
46	(random$ adj3 allocat$).tw.
47	placebo$.tw.
48	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
49	(crossover$ or (cross adj over$)).tw.
50	or/36-49
51	animal/ not human/
52	50 not 51
53	35 or 52
54	19 and 53
55	limit 54 to yr="2014-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="2014-Current"

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

#	Searches
1	(colorect* or rectal* or rectum* or anus*).tw.
2	(cancer* or neoplas* or oncolog* or malignan* or tumour* or tumor or carcinoma a* or adenocarcinoma*).tw.
3	1 AND 2
4	(bowel* or abdominoperineal or anorectal or anterior or anteroposterior or local or radical).tw.
5	(excision* or remov* or resection*).tw.
6	4 AND 5
7	(transanal* AND (microsurg* or operation or resection*)).tw.
8	(TEMS or TEM or TEO).tw.
9	(endoscop* AND (mucosal* or submucosal*)).tw.
10	6 OR 7 OR 8 OR 9 OR 10
11	3 AND 10
12	limit 11 to yr="2014-Current"

For CINAHL database:

#	Searches
1	rectal (TX All Text)
2	cancer (TX All Text)
3	resection (TX All Text)
4	excision (TX All Text)
5	3 OR 4
6	1 AND 2 AND 5
7	2014-2016 (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: - Phase II clinical trial - Non-randomised, experimental trial - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group 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

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title of Guideline	Reason why not adopted
2014	National Institute for Health and Care Excellence (NICE)	Colorectal cancer: the diagnosis and management of colorectal cancer 2014 addendum	Review question too broad and not specific enough to local vs. radical resection.

Appendix D
Excluded studies

Study	Reason for Exclusion
Arezzo 2014	Inappropriate comparator
Chakravorty 2015	Conference abstract
Clancy 2015	Included in previous guidelines
Hon 2015	Inappropriate population
Kawaguti 2014	Inappropriate comparator
Kidane 2015	Included in previous guidelines
Klos 2014	Inappropriate population
Nakamura 2015	Inappropriate comparator
Sajid 2014	Included in previous guidelines
Sajid 2014b	Conference abstract
Shaikh 2015	Included in previous guidelines
Vasiliev 2015	Conference abstract
Vendrely 2014	Conference abstract
Wang 2014	Inappropriate comparator

References: Excluded Studies

1. Arezzo A, Passera R, Saito Y, Sakamoto T, Kobayashi N, Sakamoto N, et al. Systematic review and meta-analysis of endoscopic submucosal dissection versus transanal endoscopic microsurgery for large noninvasive rectal lesions. Surg Endosc. 2014;28(2):427-38.

2. Chakravorty V, Chamberlain R, Ghlayiae N. Transanal endoscopic microsurgery (TEM) versus total mesorectal excision (TME) radical resection for T1 or T2 rectal cancer - A metaanalysis. Diseases of the Colon and Rectum. 2015;58 (5):e170.

3. Clancy C, Burke JP, Albert MR, O'Connell PR, Winter DC. Transanal endoscopic microsurgery versus standard transanal excision for the removal of rectal neoplasms: A systematic review and meta-analysis. Diseases of the Colon and Rectum. 2015;58(2):254-61.

4. Hon SS, Ng SS, Wong TC, Chiu PW, Mak TW, Leung WW, et al. Endoscopic submucosal dissection vs laparoscopic colorectal resection for early colorectal epithelial neoplasia. World journal of gastrointestinal endoscopy. 2015;7(17):1243-9.

5. Kawaguti FS, Nahas CSR, Marques CFS, Da Costa Martins B, Retes FA, Medeiros RSS, et al. Endoscopic submucosal dissection versus transanal endoscopic microsurgery for the treatment of early rectal cancer. Surgical Endoscopy and Other Interventional Techniques. 2014;28(4):1173-9.

6. Kidane B, Chadi SA, Kanters S, Colquhoun PH, Ott MC. Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. Dis Colon Rectum. 2015;58(1):122-40.

7. Klos CL, Montenegro G, Jamal N, Wise PE, Fleshman JW, Safar B, et al. Segmental versus extended resection for sporadic colorectal cancer in young patients. J Surg Oncol. 2014;110(3):328-32.

8. Nakamura F, Saito Y, Sakamoto T, Otake Y, Nakajima T, Yamamoto S, et al. Potential perioperative advantage of colorectal endoscopic submucosal dissection versus laparoscopy-assisted colectomy. Surg Endosc. 2015;29(3):596-606.

9. Sajid MS, Farag S, Leung P, Sains P, Miles WF, Baig MK. Systematic review and meta-analysis of published trials comparing the effectiveness of transanal endoscopic microsurgery and radical resection in the management of early rectal cancer. Colorectal Dis. 2014;16(1):2-14.

10. Sajid S, Leung P, Craciunas L, Miles T, Baig MK. Systematic review of studies comparing the effectiveness of trans-anal microsurgery against redical resection in the management of early rectal cancer. Surgical Endoscopy and Other Interventional Techniques. 2014;28:S21.

11. Shaikh I, Askari A, Ouru S, Warusavitarne J, Athanasiou T, Faiz O. Oncological outcomes of local excision compared with radical surgery after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and meta-analysis. International Journal of Colorectal Disease. 2014;30(1):19-29.

12. Vasiliev S, Popov D, Semenov A, Smirnova E, Savicheva E. Surgical treatment for early rectal cancer. Colorectal Disease. 2015;17:82.

13. Vendrely V, Rullier E, Rouanet P, Tuech JJ, Mosnier H, Lelong B, et al. Local excision versus total mesorectal excision in patients with good response after neoadjuvant radiochemotherapy for T2-T3 low rectal cancer: Preliminary results of the greccar 2 randomized phase 3 trial. International Journal of Radiation Oncology Biology Physics. 2014;90(1):S20.

14. Wang J, Zhang XH, Ge J, Yang CM, Liu JY, Zhao SL. Endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal tumors: A meta-analysis. World Journal of Gastroenterology. 2014;20(25):8282-7.