National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[C1] Treatment for early rectal cancer

NICE guideline TBC

Evidence reviews

July 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

Contents

1

Treatment for early rectal cancer

This evidence review supports recommendations 1.3.1 to 1.3.2.

Review question

What is the most effective treatment for early rectal cancer?

Introduction

Early rectal cancer is defined as a TNM classification of T1 or T2, N0 and M0 (National Comprehensive Cancer Network 2010). Currently, there is wide variation in practice in treatments for early rectal cancer. While treatment for early rectal cancer has typically involved anterior or abdominoperineal resection, local excision treatments have been shown to be promising for some cases of early rectal cancer (Park 2012). Minimally invasive procedures such as local excision may prevent the potential morbidity and mortality of more invasive procedures, and also result in improved rates of quality of life (Park 2012). Therefore, the aim of this review was to determine the most effective treatment for early rectal cancer.

Summary of the protocol

Please see Table 1 for a summary of the population, intervention, comparison and outcomes (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with early rectal cancer • T1 or T2 • N0 • M0

Intervention	• Transanal excision (TAE) (for example transanal endoscopic microsurgery [TEM/TEMS], transanal resection of tumour [TART], transanal minimally invasive surgery [TAMIS])
	• Total mesorectal excision (TME) (for example anterior resection, abdominoperineal resection)
	• Endoscopic resection (for example polypectomy, endoscopic submucosal dissection [ESD], endoscopic mucosal resection [EMR])
	• External radiotherapy or chemoradiotherapy with or without surgery
	  ○ Short-course
	  ○ Long-course
	• Internal radiotherapy
	  ○ Contact
	  ○ Brachytherapy

Comparison	Comparing interventions to each other
Outcomes	**Critical** • Overall survival • Local recurrence rate • Overall quality of life **Important**

	• Disease-free survival • Mortality (within 90 days) • Grade 3 or 4 complications (re-intervention or multi-organ failure)

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Nine publications from 4 RCTs and 5 retrospective cohort studies were included in this review (Barendse 2018; Chakravarti 1999; Chen 2012; Kawaguti 2014; Kiriyami 2011; Lezoche 2012; Park 2013; Winde 1997; Yan 2013).

The included studies are summarised in Table 2.

Three RCTs (Chen 2012; Lezoche 2012; Winde 1997) compared total mesorectal excision to transanal excision. One cohort study compared endoscopic resection to transanal excision (Chakravarti 1999). Four cohort studies compared transanal excision with external radiotherapy or chemoradiotherapy to transanal excision alone (Kawaguti 2014; Kiriyami 2011; Park 2013; Yan 2013).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention/Comparison	Outcomes
Comparison 1: Total mesorectal excision versus transanal excision			
Chen 2012 RCT	N=60 people with T1-2, N0, M0 rectal cancer between 6-15 cm above the	Laparoscopic lower anterior resection versus transanal	• Overall survival • Local recurrence-free survival

Study	Population	Intervention/Comparison	Outcomes
China	anal verge and the tumour was histologically determined to be moderately or highly differentiated adenocarcinoma	endoscopic microsurgery	• Grade 3 or 4 treatment complications
Lezoche 2012 RCT Italy	N=100 people with American Society of Anesthesiologists fitness grade I-II, tumour located within 6 cm of anal verge, histologically confirmed well (G1) or moderately well (G2) differentiated adenocarcinoma with a diameter no larger than 3 cm	Endoluminal locoregional excision by transanal endoscopic microsurgery versus laparoscopic total mesorectal excision	• Overall survival • Local recurrence rate • Disease-free survival • Mortality (within 90 days) • Grade 3 or 4 treatment complications
Winde 1997 RCT Germany	N=53 people with low risk rectal cancer with ≤ 4 cm diameter or sessile rectal adenomas of the lower and middle rectal third and TNM classification uT1 negative	Anterior resection versus transanal endoscopic microsurgery	• Overall survival • Local recurrence rate • Grade 3 or 4 treatment complications
Comparison 2: Endoscopic resection versus transanal excision			
Barendse 2018 RCT The Netherlands	N=209 people who had a large (≥3 cm), non-pedunculated rectal adenoma; at least 50% of the adenoma needed to be situated within 15 cm from the dentate line.	Endomucosal dissection versus transanal endoscopic microsurgery	• Overall survival • Local recurrence rate
Kawaguti 2014 Retrospective cohort study Brazil	N=24 people with early rectal cancer	Endoscopic submucosal dissection versus transanal endoscopic microsurgery	• Local recurrence rate • Grade 3 or 4 treatment complications
Kiriyami 2011 Retrospective cohort study Japan	N=85 people with preoperative diagnosis of non-invasive rectal tumours	Endoscopic submucosal dissection versus transanal anterior resection	• Local recurrence rate • Grade 3 or 4 treatment complications

Study	Population	Intervention/Comparison	Outcomes
Park 2012 Retrospective cohort study South Korea	N=63 people with non-polypoid high grade dysplasia and submucosa-invading rectal cancer	Endoscopic submucosal dissection versus transanal endoscopic microsurgery	• Local recurrence rate • Grade 3 or 4 treatment complications
Yan 2013 Retrospective cohort study China	N=54 people with tumour located less than 7 cm to anal verge and tumour size accounted < 1/3 lumen diameter; TN staged earlier than T1	Endoscopic submucosal dissection versus transanal local excision	• Local recurrence rate • Grade 3 or 4 treatment complications
Comparison 3: Transanal excision with external radiotherapy or chemoradiotherapy versus transanal excision alone			
Chakravarti 1999 Retrospective cohort study US	N=99 people with T1 or T2 rectal cancer who had undergone local excision	Local excision + adjuvant irradiation versus local excision alone	• Local recurrence-free survival

N: number; RCT: randomised controlled trial; TNM: cancer classification system, standing for tumour, nodal, or metastasis stages

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Comparison 1: Total mesorectal excision versus transanal excision

Critical outcomes

Overall survival

- Low quality evidence from 2 RCTs (N=153; median follow-up 3.6 to 9.6 years) showed no clinically important difference in overall survival between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.
- Low quality evidence from 1 RCT (N=60; median follow-up 18 months) reports no deaths in either arm when comparing total mesorectal excision to transanal excision in people with early rectal cancer.

Local recurrence

- Low quality evidence from 1 RCT (N=60; median follow-up 1.5 years) showed no clinically important difference in local recurrence free survival between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 2 RCTs (N=153; mean/median follow-up 3.6 to 9.6 years) showed no clinically important difference in local recurrence rate between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

- Low quality evidence from 1 RCT (N=100; median follow-up 9.6 years) showed no clinically important difference in disease-free survival between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.

Mortality (within 90 days)

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference in mortality (within 30 day timeframe) between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.

Grade 3 or 4 treatment complications

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference in perianal phlegmon or pelvic perionitis between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.

- Low quality evidence from 1 RCT (N=60) showed no clinically important difference in rectal perforation between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.
- Low quality evidence from 1 RCT (N=53) showed no clinically important difference in peritoneal perforation between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.
- Low quality evidence from 1 RCT (N=60) showed no clinically important difference in major bleeding (> 200 mL) between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.
- Low quality evidence from 1 RCT (N=53) showed no clinically important difference in ischemic compartment syndrome of the lower leg between receiving total mesorectal excision compared to transanal excision in people with early rectal cancer.

Comparison 2: Endoscopic resection versus transanal excision

Critical outcomes

Overall survival

- There were no events in 1 RCT (N=176; follow-up >4 years [mean/median follow-up not reported]); quality of evidence and relative effect were not estimable.
- There were no events in 1 cohort study (N=24; median follow-up 5 years); quality of evidence and relative effect were not estimable.
- There were no events in 1 cohort study (N=63; median follow-up 1.6 to 2.4 years); quality of evidence and relative effect were not estimable.
- There were no events in 1 cohort study (N=63; median follow-up 1.7 to 2.3 years); quality of evidence and relative effect were not estimable.
- There were no events in 1 cohort study (N=54; median follow-up 1.3 to 2.3 years); quality of evidence and relative effect were not estimable.

Local recurrence

- Low quality evidence from 1 RCT (N=176; mean/median follow-up not reported) showed no clinically important difference in local recurrence rates between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=24; median follow-up 5 years) showed no clinically important difference in local recurrence rates between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=63; median follow-up 4.6 years) showed a clinically important decrease in local recurrence rates between endoscopic resection compared to transanal excision in people with early rectal cancer.
- There were no events in 1 cohort study (N=63; median follow-up 1.7 to 2.3 years); quality of evidence and relative effect were not estimable.
- There were no events in 1 cohort study (N=54; median follow-up 1.3 to 2.3 years); quality of evidence and relative effect were not estimable.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

No evidence was identified to inform this outcome.

Mortality (within 90 days)

No evidence was identified to inform this outcome.

Grade 3 or 4 treatment complications

- Very low quality evidence from 1 cohort study (N=24) showed no clinically important difference in pneumothorax between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=54) showed no clinically important difference in rectal perforation between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=24) showed no clinically important difference in peritoneal perforation between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=24) showed no clinically important difference in pneumoperitoneum between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=63) showed no clinically important difference in pneumoperitoneum between endoscopic resection compared to transanal excision in people with early rectal cancer.
- Very low quality evidence from 1 cohort study (N=63) showed no clinically important difference in perforation/postoperative leakage between endoscopic resection compared to transanal excision in people with early rectal cancer.

Comparison 3: Transanal excision with external radiotherapy or chemoradiotherapy versus transanal excision alone

Critical outcomes

Overall survival

No evidence was identified to inform this outcome.

Local recurrence

- Very low quality evidence from 1 cohort study (N=99; median follow-up 4.3 years) showed no clinically important difference in local recurrence free survival between receiving transanal excision with external radiotherapy or chemoradiotherapy compared to transanal excision alone in people with early rectal cancer.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

No evidence was identified to inform this outcome.

Mortality (within 90 days)

No evidence was identified to inform this outcome.

Grade 3 or 4 complications

No evidence was identified to inform this outcome.

Comparison 4: Internal radiotherapy versus transanal excision

No evidence was identified to inform this comparison.

Comparison 5: Total mesorectal excision versus endoscopic resection

No evidence was identified to inform this comparison.

Comparison 6: Total mesorectal excision versus internal radiotherapy

No evidence was identified to inform this comparison.

Comparison 7: Endoscopic resection versus external radiotherapy or chemoradiotherapy with or without surgery

No evidence was identified to inform this comparison.

Comparison 8: Endoscopic resection versus internal radiotherapy

No evidence was identified to inform this comparison.

Comparison 9: Total mesorectal excision versus internal radiotherapy

No evidence was identified to inform this comparison.

Comparison 10: External radiotherapy or chemoradiotherapy with or without surgery versus internal radiotherapy

No evidence was identified to inform this comparison.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Overall survival and local recurrence were considered critical outcomes for decision making because local recurrence suggests ineffective treatment of the early rectal cancer, potentially requiring further treatment and affecting overall survival. Overall quality of life was also a critical outcome because of the impact of disease recurrence on patients and the potential long term adverse effects of the treatments considered.

Disease-free survival and treatment complications were considered important outcomes.

The quality of the evidence

Evidence was available for the comparison of total mesorectal excision versus transanal excision, endoscopic resection versus transanal excision, transanal excision versus external radiotherapy or chemoradiotherapy. No evidence was found comparing internal radiotherapy versus transanal excision, total mesorectal excision versus endoscopic resection, total mesorectal excision versus internal radiotherapy, endoscopic resection versus external radiotherapy or chemoradiotherapy with or without surgery, endoscopic resection versus internal radiotherapy, total mesorectal excision versus internal radiotherapy, or external radiotherapy or chemoradiotherapy with or without surgery versus internal radiotherapy. A network meta-analysis was considered but was not possible due to the limited available evidence and the limitations in the evidence discussed below.

Evidence was available for all of the outcomes except quality of life. The quality of the evidence was assessed using GRADE and varied from low to very low quality. The quality of evidence was most often downgraded because of methodological limitations affecting the risk of bias, indirectness of the study population, and imprecision around the risk estimate.

Methodological limitations affecting the risk of bias were generally attributable to lack of or unclear randomisation, allocation and outcome assessment blinding, and lack of controlling for confounders. Indirectness of the study population was attributable to a proportion of the sample having lymphatic involvement at baseline. Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes.

The largest of the included RCTs was a non-inferiority trial and not powered to determine the most effective treatment. Given that, even when pooled together, the remaining studies had much smaller sample sizes than this trial, the committee was unable to conclude with confidence whether one treatment was better than the other.

The quality of the evidence for some of the outcomes was not assessable due to the data being presented as medians or zero events in both treatment arms.

The low quality of the evidence, and lack of evidence for many comparisons, affected the decision-making and the strength of the recommendations as there was insufficient evidence to recommend one type of treatment over another.

Benefits and harms

While the evidence did not favour one treatment over the other, the committee were aware of risks and benefits of each approach.

TAE, including transanal minimally invasive surgery (TAMIS) and transanal endoscopic microsurgery (TEMS), needs a general anaesthetic, may require conversion to an open or laparoscopic procedure and may have postoperative complications. However, benefits include it being a minimally invasive procedure (no external scars) requiring no resection of the bowel, and therefore better functional results, shorter hospital stay and the avoidance of a stoma. It also allows for a full thickness excision of the lesion.

ESD may need further surgery depending on histology and prevents a full thickness excision. However, benefits include the fact that it is a minimally invasive procedure that can be performed with sedation instead of general anaesthesia, does not require the resection of the bowel and therefore has better functional results, has shorter hospital stays (can be performed as a day case) and avoids the need for a stoma.

TME may require conversion to an open procedure, have significant postoperative complications, including anastomotic leak, pelvic abscess, anastomotic stricture and bleeding, injury to neighbouring structures, require a potentially permanent stoma, lead to incisional hernia, adhesions, sexual and bowel dysfunction and require a longer hospital stay. However, while TME is associated with higher morbidity, it can give better curative results as it also removes lymph nodes which allows for accurate staging of the cancer and whether adjuvant treatment is required. Furthermore TME can be done with a minimally invasive technique (laparoscopic or robotic).

The committee highlighted that the key point on deciding which technique to use is the risk of residual disease, specifically, lymph node involvement. A local excision (TAE and ESD) will not remove the lymph nodes whereas a TME does. Furthermore, until the lesion is resected, staging is based on radiological investigations. From their clinical experience, the committee noted that most patients would favour a local excision over a TME. However, if histological features of the local excision specimen determine a high risk of nodal disease, then a TME procedure would subsequently be recommended. Additionally, TME may be discussed from the outset if initial staging scans indicate the need for a more invasive procedure or the patient indicates interest for a single, definitive procedure.

The committee considered that a potential benefit of the recommendations could be the increased use of TEM or ESD, with fewer treatment-related adverse events than TME. Potential risks include over-treatment with TME, or radiotherapy, and contention over the effectiveness of treatments. The committee balanced these harms against the benefits by recommending a discussion of the likely implications of treatments to help patients bring their own values and preferences into the treatment decision. Because the evidence did not favour one treatment option over another one, a shared decision about which treatment to have should be based on the person's preferences, taking into consideration the implications of each of these treatments, including potential benefits, risks and practical factors.

No evidence was available on the effectiveness of preoperative radiotherapy for people with early rectal cancer. Based on the committee's expertise, they made a consensus recommendation about not offering preoperative radiotherapy for these people unless in a context of a clinical trial. The committee was aware of the ongoing STAR-TREC trial comparing total mesorectal excision to either long-course or short-course chemoradiotherapy.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The recommendations partly reflect current practice as the three options that have been recommended (ESD, TAE [including TAMIS and TEMS] and TME) are the treatments that are most frequently used. However, while the recommendation does not suggest a preference for one technique other another, it is possible that it may result in the increased use of ESD. An increase in resources may be required to provide ESD in centres where it is not currently available. This could include the cost of training staff as well as the equipment costs. However, it's unlikely to require a substantial increase in resources as many centres are likely to continue using other techniques.

Other factors the committee took into account

No areas of the review or recommendations need specific attention with regard to equalities issues.

Given the low quality of the published evidence the committee discussed making research recommendations about the effects of interventions for early rectal cancer on patient-reported quality of life and about how interventions could be selected for patients. Following their discussion the committee decided not to make any research recommendations for this topic, partly because it was not a priority in comparison to the other research topics within this guideline and also because the some of the interventions of interest were already being compared in the ongoing STAR-TREC trial.

References

Barendse 2018

Barendse R, Musters G, de Graaf E, et al. (2018) Randomised controlled trial of transanal endoscopic microsurgery versus endoscopic mucosal resection for large rectal adenomas (TREND Study). Gut 67(5): 837-846

Chakravarti 1999

Chakravarti A, Compton C, Shellito P, et al. (1999) Long-term follow-up of patients with rectal cancer managed by local excision with and without adjuvant irradiation. Annals of Surgery 230(1): 49-54

Chen 2013

Chen Y, Liu Z, Zhu K, et al. (2013) Transanal endoscopic microsurgery versus laparoscopic lower anterior resection for the treatment of T1-2 rectal cancers. Hepato-Gastroenterology 60(124): 727-32

Kawaguti 2014

Kawaguti F, Nahas C, Marques C, et al. (2014) Endoscopic submucosal dissection versus transanal endoscopic microsurgery for the treatment of early rectal cancer. Surgical Endoscopy and Other Interventional Techniques 28(4): 1173-1179

Kiriyami 2011

Kiriyama S, Saito Y, Matsuda T, et al. (2011) Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumour: A retrospective study. Journal of Gastroenterology and Hepatology 26(6): 1028-1033

Lezoche 2012

Lezoche E, Baldarelli M, Lezoche G, et al. (2012) Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. British Journal of Surgery 99(9): 1211-1218

National Comprehensive Cancer Network 2010

National Comprehensive Cancer Network (2010) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 1

Park 2012

Park S, Min Y, Shin J, et al. (2012) Endoscopic submucosal dissection or transanal endoscopic microsurgery for nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer. Endoscopy 44(11): 1031-1036

Winde 1997

Winde G, Blasius G, Herwig R, et al. (1997) Benefit in therapy of superficial rectal neoplasms objectivized: Transanal endoscopic microsurgery (TEM) compared to surgical standards. Minimally Invasive Therapy and Allied Technologies 6(4): 315-323

Yan 2016

Yan F, Lou Z, Hu S, et al. (2016) Endoscopic submucosal dissection versus transanal local excision for rectal carcinoid: A comparative study. World Journal of Surgical Oncology 14(1): 162

1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: What is the most effective treatment 4 for early rectal cancer?

5 **Table 3: Review protocol for effective treatment for early rectal cancer**

Field (based on PRISMA-P)	Content
Review question in guideline	What is the most effective treatment for early rectal cancer?
Type of review question	Intervention
Objective of the review	To determine the most effective treatment for early rectal cancer.
Eligibility criteria – population/disease/condition/issue/domain	Adults with early rectal cancer Early rectal cancer defined by the guideline committee according to the TNM classification as: • T1 or T2 • N0 • M0 Tumour staging determined by ultrasound or MRI. Rectal cancer defined as any tumour within 15 cm from anal verge excluding anal canal.

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Transanal excision (TAE) (for example transanal endoscopic microsurgery [TEM/TEMS], transanal resection of tumour [TART], transanal minimally invasive surgery [TAMIS])
	• Total mesorectal excision (TME) (for example anterior resection, abdominoperineal resection)
	• Endoscopic resection (for example polypectomy, endoscopic submucosal dissection [ESD], endoscopic mucosal resection [EMR])
	• External radiotherapy or chemoradiotherapy with or without surgery
	  ○ Short-course
	  ○ Long-course
	• Internal radiotherapy
	  ○ Contact
	  ○ Brachytherapy

Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparing interventions to each other
Outcomes and prioritisation	**Critical outcomes:** • Overall survival (MID: statistical significance)

Field (based on PRISMA-P)	Content
	• Local recurrence rate (MID: statistical significance) • Overall quality of life measured using validated scales (MID: published MIDs from literature, see below) **Important outcomes:** • Disease-free survival (MID: statistical significance) • Mortality (within 90 days) (MID: statistical significance) • Grade 3 or 4 complications (i.e. re-intervention or multi-organ failure) (MID: statistical significance) Quality of Life MIDs from the literature: • EORTC QLQ-C30: 5 points • EORTC QLQ-CR29: 5 points • EORTC QLQ-CR38: 5 points • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points • FACT-G: 5 points • 12 Item Short Form Survey (SF-12): >3.77 for the mental component summary (MCS) and >3.29 for the physical component summary (PCS) • 36 Item Short Form Survey (SF-36): >7.1 for the physical functioning scale, >4.9 for the bodily pain scale, and >7.2 for the physical component summary
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Comparative observational studies (if insufficient RCTs for the critical outcomes)
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post 1997 Observational studies should include multivariate analysis controlling for the following confounding factors: • Age • Performance status • Tumour location • Clinical stage • Tumour grade • Lymphovascular invasion (for surgery studies) • Perineural invasion (for surgery studies)

Field (based on PRISMA-P)	Content
	• Completeness of resection (for surgery studies) • Tumour size (for surgery studies) Studies conducted post 1997 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 1997 would not be relevant any longer.
Proposed sensitivity/sub-group analysis, or meta-regression	In case of heterogeneity, the following subgroup analyses will be conducted: • Tumour stage 1 or 2 • Age
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched (to be confirmed by the Information Scientist): Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance, but download all results • Dates: from 1997
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).

Field (based on PRISMA-P)	Content
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • ROBINS-I for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. MIDs: The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P)	Content
	Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1: methods.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; M0: distant metastasis stage; MID: minimal important difference; MRI: magnetic resonance imaging; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; PROSPERO: International prospective register of systematic review; RCT: randomised controlled trial; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROBIS: a tool for assessing risk of bias in systematic reviews; TNM: cancer classification system standing for tumour, node, metastasis

Appendix B – Literature search strategies

Literature search strategies for review question: What is the most effective treatment for early rectal cancer?

A combined search was conducted for the following three review questions:

- What is the most effective treatment for early rectal cancer?
- What is the effectiveness of preoperative radiotherapy or chemoradiotherapy for rectal cancer?
- What is the optimal surgical technique for rectal cancer?

Database: Embase/Medline

Last searched on: 12/02/2019

#	Search
1	exp Rectal Neoplasms/ use prmz
2	*rectum cancer/ or *rectum tumour/
3	2 use oemezd
4	exp Adenocarcinoma/
5	(T1 or T2 or N0 or M0).ti,ab.
6	1 or 3
7	4 or 5
8	6 and 7
9	((rectal or rectum) adj3 (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)).ti,ab.
10	early rect* cancer.ti,ab.
11	6 or 8 or 9 or 10
12	exp radiotherapy/ or exp radiation oncology/ or exp external beam radiotherapy/ or exp Brachytherapy/ or exp preoperative care/ or exp neoadjuvant therapy/ or exp multimodality cancer therapy/ or exp chemotherapy/ or exp antineoplastic agent/ or exp drug therapy/ or exp chemoradiotherapy/ or exp fluorouracil/ or exp folinic acid/ or exp capecitabine/ or exp oxaliplatin/ or exp bevacizumab/ or exp methotrexate/ or exp radiation dose fractionation/ or exp tumour recurrence/
13	12 use oemezd
14	exp Radiotherapy/ or exp Radiation Oncology/ or exp Radiotherapy, Computer-Assisted/ or exp Brachytherapy/ or exp Preoperative Care/ or exp Neoadjuvant Therapy/ or exp Combined Modality Therapy/ or exp Chemoradiotherapy/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Drug Therapy/ or exp Antineoplastic Agents/ or exp Fluorouracil/ or exp Leucovorin/ or exp Capecitabine/ or exp Bevacizumab/ or exp Methotrexate/ or exp Dose Fractionation/
15	14 use prmz
16	((radiotherap* or chemoradio* or radiation or brachytherapy* or chemotherapy*) adj (pre?op* or preop* or periop* or neoadjuvant)).ti,ab.
17	(5-fluorouracil or 5-FU or leucovorin or folinic acid or capecitabine or oxaliplatin or bevacizumab or methotrexate or dose* or fraction* or recurren*).ti,ab.
18	13 or 15 or 16 or 17
19	exp Laparoscopy/ or exp Transanal Endoscopic Microsurgery/ or exp Minimally Invasive Surgical Procedures/ or exp Endoscopy/ or exp Endoscopic Mucosal Resection/ or exp Surgical Procedures, Operative/ or exp Robotic Surgical Procedures/ or exp Surgery, Computer-Assisted/ or exp Dissection/
20	19 use prmz
21	exp laparoscopy/ or exp endoscopic surgery/ or exp transanal endoscopic microsurgery/ or exp endoscopy/ or exp minimally invasive surgery/ or exp endoscopic mucosal resection/ or exp surgery/ or exp robotic surgical procedure/ or exp computer assisted surgery/ or exp dissection/ or exp total mesorectal excision/ or exp excision/ or exp rectum resection/ or exp endoscopic polypectomy/ or exp polypectomy/ or exp endoscopic submucosal dissection/
22	21 use oemezd
23	(laparoscop* or endoscop* or transanal excision* or TAE or transanal endoscopic microsurger* or TEM or TEMS or transanal resection or TART or transanal minimally invasive surger* or TAMIS or total mesorectal excision* or TaTME or transanal total mesorectal excision* or TME or anterior resection* or abdominoperineal resection* or endoscopic resection* or polypectomy or endoscopic submucosal dissection* or ESD or endoscopic mucosal resection* or EMR or surger* or surgic* or operat*).ti,ab.
24	20 or 22 or 23
25	11 and 18
26	11 and 18 and 24
27	25 or 26
28	limit 27 to english language
29	limit 28 to yr="1997 -Current"
30	(conference abstract or letter).pt. or letter/ or editorial.pt. or note.pt. or case report/ or case study/ use oemezd
31	Letter/ or editorial/ or news/ or historical article/ or anecdotes as topic/ or comment/ or case report/ use prmz
32	(letter or comment* or abstracts).ti.

#	Search
33	or/30-32
34	randomized controlled trial/ use prmz
35	randomized controlled trial/ use oemezd
36	random*.ti,ab.
37	or/34-36
38	33 not 37
39	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ use prmz
40	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ use oemezd
41	(rat or rats or mouse or mice).ti.
42	38 or 39 or 40 or 41
43	29 not 42
44	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
45	44 use prmz
46	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
47	46 use oemezd
48	or/45,47
49	43 and 48
50	epidemiologic studies/ or observational study/ or case control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/
51	50 use prmz
52	exp observational study/ or exp case control study/ or exp retrospective study/ or exp cohort analysis/ or exp longitudinal study/ or exp follow up/ or exp prospective study/ or exp cross-sectional study/
53	52 use oemezd
54	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys*)).ti.
55	51 or 53 or 54
56	43 and 55
57	49 or 56
58	57 not 56
59	56 or 58

1 **Database: Cochrane Library**

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Rectal Neoplasms] explode all trees
2	MeSH descriptor: [Adenocarcinoma] explode all trees
3	T1 or T2 or N0 or M0
4	#2 or #3
5	#1 and #4
6	(rectal or rectum) near (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)
7	early rect* cancer
8	#1 or #5 or #6 or #7
9	MeSH descriptor: [Radiotherapy] explode all trees
10	MeSH descriptor: [Radiation Oncology] explode all trees
11	MeSH descriptor: [Radiotherapy, Computer-Assisted] explode all trees
12	MeSH descriptor: [Brachytherapy] explode all trees
13	MeSH descriptor: [Preoperative Care] explode all trees
14	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
15	MeSH descriptor: [Combined Modality Therapy] explode all trees
16	MeSH descriptor: [Chemoradiotherapy] explode all trees
17	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
18	MeSH descriptor: [Drug Therapy] explode all trees
19	MeSH descriptor: [Antineoplastic Agents] explode all trees
20	MeSH descriptor: [Fluorouracil] explode all trees
21	MeSH descriptor: [Capecitabine] explode all trees
22	MeSH descriptor: [Bevacizumab] explode all trees
23	MeSH descriptor: [Methotrexate] explode all trees
24	MeSH descriptor: [Dose Fractionation] explode all trees
25	(radiotherap* or chemoradio* or radiation or brachytherapy* or chemotherapy*) near (pre?op* or preop* or periop* or neoadjuvant)
26	5-fluorouracil or 5-FU or leucovorin or folinic acid or capecitabine or oxaliplatin or bevacizumab or methotrexate or dose* or fraction* or recurren*
27	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26

#	Search
28	MeSH descriptor: [Laparoscopy] explode all trees
29	MeSH descriptor: [Transanal Endoscopic Microsurgery] explode all trees
30	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
31	MeSH descriptor: [Endoscopy] explode all trees
32	MeSH descriptor: [Endoscopic Mucosal Resection] explode all trees
33	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
34	MeSH descriptor: [Robotic Surgical Procedures] explode all trees
35	MeSH descriptor: [Surgery, Computer-Assisted] explode all trees
36	MeSH descriptor: [Dissection] explode all trees
37	laparoscop* or endoscop* or transanal excision* or TAE or transanal endoscopic microsurger* or TEM or TEMS or transanal resection or TART or transanal minimally invasive surger* or TAMIS or total mesorectal excision* or TME or anterior resection* or abdominoperineal resection* or endoscopic resection* or polypectomy or endoscopic submucosal dissection* or ESD or endoscopic mucosal resection* or EMR or surger* or surgic* or operat*
38	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
39	#8 and #27
40	#8 and #27 and #38
41	#39 or #40 Publication Year from 1997 to 2017

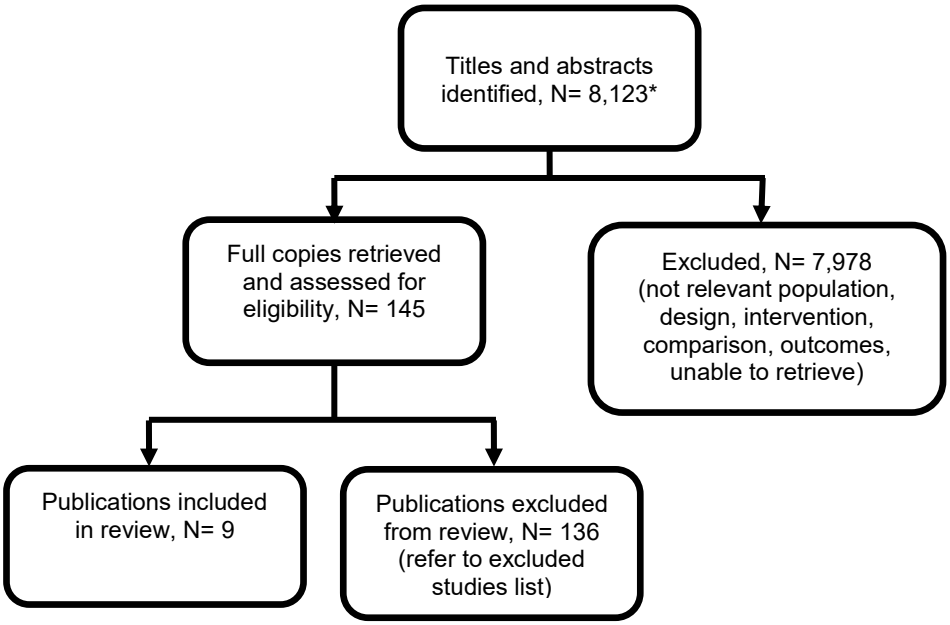
1

2

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the most effective treatment for early rectal cancer?

Figure 1: Study selection flow chart



**The literature search was done for 3 review questions at once including the current review and reviews 'What is the most effective treatment for early rectal cancer?' and 'What is the optimal surgical technique for rectal cancer after preoperative radiotherapy or chemoradiotherapy?'. The number of titles and abstracts identified applies for all three reviews but all the other numbers are applicable to this specific review only. In addition, possibly relevant studies were added from systematic reviews.*

1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: What is the most effective treatment for early rectal cancer?

3 **Table 4: Clinical evidence tables**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Barendse RM, Musters GD, de Graaf EJR, van den Broek FJC, Consten ECJ, Doornebosch PG, Hardwick JC, de Hingh IHJT, Hoff C, Jansen JM, van Milligen de Wit AWM, van der Schelling GP, Schoon EJ, Schwartz MP, Weusten BLAM, Dijkgraaf MG, Fockens P, Bemelman WA, Dekker E; TREND Study group. Randomised controlled trial of transanal endoscopic microsurgery versus endoscopic mucosal resection for large rectal adenomas (TREND Study). Gut. 2018 May;67(5):837-846. **Ref Id**	**Sample size** N=209 randomised (204 included in the analysis) N=176 ITT analysis **Characteristics** Male: n (%): 48 (54) (EMR) vs 47 (53) (TEMS) Age years (SD): 67.4 ±11.3 (EMR) vs 67.5 (±10.0) (TEMS) Adenoma distance from anal verge (mm ± SD): 4.9 ± 3.8 (EMR) vs 5.5 ± 4.4 (TEMS) **Inclusion criteria** Patients above 17 years of age, who had a large (≥3 cm), non-pedunculated rectal adenoma; at least 50% of the	**Interventions** TEMS: TEMS was performed as described by Buess. The rectal defect was closed in the transverse direction. When TEMS turned out to be technically impossible after randomisation, patients underwent subsequent EMR EMR: was performed as described by Karita and Hurlstone and argon plasma coagulation of the edges of the mucosal defect was prescribed in the protocol.14–16 When it turned out that EMR was technically not possible after randomisation or when EMR failed to remove >90% of the adenoma, the patient subsequently underwent TEMS	**Details** Randomisation: Computer-generated block randomisation with a 1:1 allocation ratio and concealed random block sizes of two, four and six patients were used. Randomisation was stratified according to primary or recurrent nature of adenoma Blinding: Due to the invasive nature of the interventions and the logistics involved, neither the trial participants nor the investigators could be masked to group allocation. Follow-up: After 3 months, follow-up endoscopy was performed for	**Results** Outcome: overall survival After a follow-up of more than 4 years overall survival was 100% (mean /median follow-up not reported) Outcome: recurrence rate 15% EMR vs 11% TEMS (RR 1.33 95% upper limit 2.46). (The median time to recurrence was 7 months (IQR 6–12) after EMR and 12 months (IQR 7–21) after TEMS (p=0.10))	**Limitations** Cochrane risk of bias Selection bias Random sequence generation: low risk (random were computer generated) Allocation concealment: high risk (allocation unmasked) Performance bias Blinding of participants and personnel: high risk (open label) Detection bias Blinding of outcome assessment: unclear risk (not reported, but likely not blinded) Attrition bias Incomplete outcome data: low risk (ITT population) Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
982330 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To compare the cost-effectiveness and cost-utility of transanal endoscopic microsurgery (TEMS) and endoscopic mucosal resection (EMR) for the resection of large rectal adenomas **Study dates** February 2009 to September 2013 **Source of funding** The trial was sponsored by the Netherlands Organization for Health Research and Development (ZonMw, file number 17092201), which did not have access to outcome data during the trial and	adenoma needed to be situated within 15 cm from the dentate line. All patients underwent white light endoscopy; adenomas were endoscopically assessed for any malignant features. In case of any suspicious features, endorectal ultrasound (EUS) was allowed to evaluate for deep submucosal invasion. EUS was not mandatory in the diagnostic workup. Biopsies of the lesion, if taken, did not show submucosal invasion at histopathological evaluation. **Exclusion criteria** Patients with a suspicion of malignancy based on endoscopic features, biopsies or EUS, as well as patients with a life-threatening systemic disease or moribund clinical condition		assessment of potential adenoma remnants. Statistical methods: The principal analysis consisted of an ITT comparison of recurrence rates in the two treatment groups. The goal was to test for non-inferiority of EMR with respect to the primary outcome, and superiority with respect to secondary outcomes. The margin of non-inferiority applied in the TREND Study was 6.7%. It was assumed that the recurrence rate in the TEMS group would be 3.3% and that EMR would be considered non-inferior if the recurrence percentage would remain below 10% at maximum.14 Assuming a baseline recurrence rate of 3.3% for both TEMS and EMR, we would consider EMR to be non-inferior if the associated recurrence rate was less than 6.7 percentage points above the TEMS recurrence percentage.		Selective reporting: low risk (primary outcome points were reported) Other bias None **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
did not participate in data analyses or the preparation of the manuscript. No endoscopic or surgical equipment was donated by the manufacturer	(ASA classification IV–V), a non-correctable coagulopathy or other contraindications for rectal surgery were excluded.		We used a one-sided significance level of 0.05. To attain a power of 80%, 89 patients were needed in each group. The χ2 test was applied to compare recurrence rates. The number of days not spent in hospital was compared by the Wilcoxon rank-sum test. Quality of life questionnaires were analysed using linear mixed models.		
Full citation Chakravarti, A., Compton, C. C., Shellito, P. C., Wood, W. C., Landry, J., Machuta, S. R., Kaufman, D., Ancukiewicz, M., Willett, C. G., Long-term follow-up of patients with rectal cancer managed by local excision with and without adjuvant irradiation, Annals of Surgery, 230, 49-54, 1999 **Ref Id** 746093	**Sample size** N=99 LE alone=52 LE + EBRT=47 **Characteristics** LE alone (n=52) Follow-up, months, median (IQR)= 51 (4-162) T1 stage, n (%)=44 (85) T2 stage, n (%)= 8 (15) LE + EBRT (n=47) Follow-up, months, median (IQR)= 51 (4-162)	**Interventions** Local excision (LE) alone vs LE+ external beam radiotherapy (EBRT) LE= surgical procedures included local excision with a transanal or transsphincteric approach, excision through a midline posterior proctoctomy, or transanal fulguration LE + EBRT= Mean dose was 53.6 Gy (range 45 to 64.8). 45/47 received postoperative irradiation, 2/47 received preoperative irradiation.	**Details** Randomisation N/A Blinding N/A Follow-up/outcomes Outcomes: Local failure, distant metastasis, and survival after treatment Follow up: Mean and median follow up times for both groups were 51 months from surgery (range 4 to 162) Statistical analysis	**Results** Outcome: Local recurrence free survival (median follow up 51 months); event is local recurrence LE + EBRT, n/total= 19/47 (66%) LE alone= 18/52 (74%) p= 0.18 5-year actuarial free survival rate LE + EBRT= 90% LE alone= 72% Median follow up time= 51 months	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias due to confounding (There is potential for confounding, study did not control for confounders such as age or sex, but did assess outcomes according to treatment, tumour stage, and pathological features.) Bias in selection of participants into the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out US **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to measure the long-term outcomes of patients undergoing local excision for T1 or T2 rectal cancers. **Study dates** January 1966 to January 1997 **Source of funding** Not reported	T1 stage, n (%)=14 (30) T2 stage, n (%)=33 (70) Overall (n=99) Age, years, median (IQR)= 68 (38-91) Male, n (%)= 54 (55) **Inclusion criteria** T1 or T2 rectal cancers Underwent local excision **Exclusion criteria** Not reported	45 Gy was delivered to the pelvic field in 25 fractions using a four-field technique over 5 to 6 weeks. Tumour volume was boosted with photons, protons, or interstitial implants. Boost doses > 55 Gy were generally given for patients with tumour involvement of the surgical margins. Patients who received chemotherapy received fluorouracil chemotherapy with pelvic irradiation via intravenous fluorouracil (500mg/m2) for 3 straight days during the first and last week of radiation treatment.	Kaplan-Meier methods used to calculate actuarial recurrence free survival rates and local control rates. Outcome parameters assessed according to treatment, tumour stage, and pathological features.		study: Serious risk of selection bias (Study did not report patient characteristics per treatment group. 'The results are interpreted in view of the higher T-stage distribution and high-risk pathologic features of the patients in the irradiated group') At intervention Bias in classification of interventions: Moderate risk of bias (Unclear whether information used to define intervention groups was specified at the start of the intervention. Intervention groups were clearly defined.) Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias due Bias in measurement of outcomes: Low risk of bias (Outcomes were objective and measured

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					by health care professionals, not participant recall) Bias in selection of the reported result: Low risk of bias **Other information** None
Full citation Chen, Y. Y., Liu, Z. H., Zhu, K., Shi, P. D., Yin, L., Transanal endoscopic microsurgery versus laparoscopic lower anterior resection for the treatment of T1-2 rectal cancers, Hepato-Gastroenterology, 60, 727-32, 2013 **Ref Id** 746183 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** The aim of the study was to assess the	**Sample size** n= 60 LAR= 30 TEMS= 30 **Characteristics** LAR (n=30) Male gender, n (%) 17 (57) Age, years, mean (SD) 66.2 (7.7) Tumour size, cm, mean (SD) 2.8 (0.6) Tumour distance above anal verge, cm, mean (SD) 8.1 (1.3) Tumour stage T1, n (%) 22 (73.3) Tumour stage T2, n (%) 8 (26.7) TEMS (n=30)	**Interventions** LAR vs TEMS LAR: a standard f-trocar technique was used, including high-level transection of the inferior mesenteric artery, medial-to-lateral mobilisation of the descending colon, high-level transection of the inferior mesenteric vein, mobilisation of the splenic flexure, TME using sharp dissection at the pelvic floor and mechanical side-to-end coloanal anastomises using mechanical stapling devices. TEMS: The tumour was excised using an electrosurgical dissector under an electronic	**Details** Randomisation "Patients were assigned to TEMS or LAR in a random and equal way" Blinding Not blinded Follow-up/outcomes Primary outcome measures included operative time, conversion rate, mortality, local recurrence and distant metastasis. Patients were followed up twice a year for the first 5 years. Statistical analysis Quantitative data was expressed as means (SD) and was analysed	**Results** Outcome: Overall survival (median follow up 18 months); event is death LAR= 0/30 TEMS, n/total= 0/30 Outcome: Local recurrence free survival (median follow up 18 months); event is local recurrence LAR= 0/30 TEMS, n/total= 2/30* p= 0.229 Outcome: Rectal perforation, n/total LAR= 0/30 TEMS= 2/30 Outcome: Major bleeding (> 200 mL), n/total LAR= 1/30 TEMS= 0/30	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk (random were computer generated) Allocation concealment: unclear risk (not reported) Performance bias Blinding of participants and personnel: high risk (open label) Detection bias Blinding of outcome assessment: unclear risk (not reported, but likely not blinded) Attrition bias Incomplete outcome data: unclear risk (no mention of intention-to-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
effectiveness of transanal endoscopic microsurgery (TEMS) compared to laparascopic lower anterior resection (LAR) to treat rectal cancer. **Study dates** January 2008 to December 2010 **Source of funding** Shanghai Municipal Department of Health	Male gender, n (%) 14 (47) Age, years, mean (SD)= 68.8 (5.3) Tumour size, cm, mean (SD) 2.3 (0.5) Tumour distance above anal verge, cm, mean (SD) 7.8 (1.6) Tumour stage T1, n (%) 24 (80) Tumour stage T2, n (%) 6 (20) **Inclusion criteria** Rectal cancer staged at T1-2, N0, M0 Tumour located between 6 and 15 cm above the anal verge Tumour was histologically determined to be moderately or highly differentiated adenocarcinoma Patients had not undergone lower abdominal or pelvic physical tolerance on routine	endoscope. The resection margin was > 0.5-1.0 cm away from the tumour margin. TEMS was immediately converted to salvage LAR in the case of rectal perforation or positive resection margins	using Student's t-tests. Qualitative data were expressed as n (%) and analysed using Fisher's exact probability test. Survival curves were estimated using Kaplan-Meier curves. $p < 0.05$ was considered statistically significant.	*data extracted from total randomised sample	treat approach to analysis. 2 patients not accounted for in TEMS arm in follow up) . Reporting bias Selective reporting: low risk (primary outcome points were reported) Other bias None **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	preoperative assessment **Exclusion criteria** Presence of distant metastases Tumour invasion into deep muscle layer or regional lymph nodes				
Full citation Kawaguti, F. S., Nahas, C. S. R., Marques, C. F. S., Da Costa Martins, B., Retes, F. A., Medeiros, R. S. S., Hayashi, T., Wada, Y., De Lima, M. S., Uemura, R. S., Nahas, S. C., Kudo, S. E., Maluf-Filho, F., Endoscopic submucosal dissection versus transanal endoscopic microsurgery for the treatment of early rectal cancer, Surgical Endoscopy and Other Interventional Techniques, 28, 1173-1179, 2014 **Ref Id** 748054	**Sample size** n= 24 ESD= 11 TEMS= 13 **Characteristics** ESD (n=11) Age, years, mean (SD)= 62.3(4.6) Tumour size, mm, mean (SD)= 64.6 (57.9) Tumour distance above anal verge, mm, mean (SD)= 2.72 (2.19) TEMS (n=13) Age, years, mean (SD)= 61.5 (9.5) Tumour size, mm, mean (SD)= 43.9 (30.7) Tumour distance above anal verge,	**Interventions** ESD vs TEMS ESD: Circumferential incision and submucosal dissection was performed. TEMS: TEMS was performed on those with lesions restricted to the submucosal layer. Position of the patient depended on the location of the tumour. Carbon dioxide was insufflated to enlarge the intrarectal space, followed by full-thickness resection and then continuous suture.	**Details** Randomisation N/A Blinding N/A Follow-up/outcomes Follow up: Follow up colonoscopy 3 months and 6 months after original procedure. Outcomes: en bloc resection rate, early and late complications, histological diagnosis, procedural time, length of hospital stay Statistical analysis T-test or Fisher's exact test. P-value of < 0.05 was statistically significant	**Results** Outcome: Local recurrence, n/total ESD= 1/11 TEMS= 2/13 Outcome: Pneumothorax, n/total ESD= 2/11 TEMS= 0/13 Outcome: Perforation of peritoneum, n/total ESD= 0/11 TEMS= 2/13 Outcome: Pneumoperitoneum, n/total ESD= 0/11 TEMS= 1/13	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Critical risk of bias due to confounding (There is potential for confounding, for example age, but the study did not report controlling for these variables in the analysis) Bias in selection of participants into the study: Serious risk of selection bias (Patient selection was retrospective. The analysis does not account for characteristics, such as age, and sex. 'Patients

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Brazil **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the efficacy of endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgry (TEMS) in the treatment of early rectal cancer **Study dates** July 2008 to October 2011 **Source of funding** No financial ties to disclose	mm, mean (SD)= 2.85 (2.88) **Inclusion criteria** Early rectal cancer **Exclusion criteria** Not reported				with larger lesions or lesions located more proximally in in the rectum were preferably sent for an ESD.') At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias (The study was retrospective in nature, but all of the outcomes were objective and would not be affected by bias in recall) Bias due to missing data: Low risk of bias (All patients accounted for in analysis) Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					None
Full citation Kiriyama, S., Saito, Y., Matsuda, T., Nakajima, T., Mashimo, Y., Joeng, H. K., Moriya, Y., Kuwano, H., Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumour: A retrospective study, Journal of Gastroenterology and Hepatology (Australia), 26, 1028-1033, 2011 Ref Id 748244 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to compare the clinical efficacy between endoscopic submucosal dissection (ESD) and transanal resection (TAR) for	**Sample size** n= 85 ESD= 52 TAR= 33 **Characteristics** ESD (n=52) Age, years, mean (SD)= 61 (11) Tumour size, mm, mean (SD)= 40 (21) Procedure time, min, mean (SD)= 131 (100) TAR (n=33) Age, years, mean (SD)= 64 (13) Tumour size, mm, mean (SD)= 39 (24) Procedure time, min, mean (SD)= 63 (54) **Inclusion criteria** Preoperative diagnosis of non-invasive rectal tumours **Exclusion criteria** Not reported	**Interventions** ESD vs TAR ESD: indigo carmine dye was sprayed; glycerol and sodium hyaluronic acid injected into submucosal layer; cut made with bipolar current needle knife; complete circumferential incision; submucosal dissection done TAR: patients were in the prone jack knife position or lithotomy position. No indigo carmine dye used. Sale solution with epinephrine was injected into the submucosal layer. A full thickness excision was performed if a submucosal deep invasion was suspected	**Details** Randomisation Non-randomised retrospective cohort study. 85 patients were treated with ESD or TAR. Blinding Not blinded. Data from the database and pathological reports were analysed retrospectively Follow-up/outcomes Outcomes: en-bloc resection rate, local recurrence rate, early and late complications, histological diagnosis, procedure time, length of hospital stay. Follow up: 6 months post-treatment Statistical analysis X2 test or t-test. P-value of < 0.05 considered statistically significant.	**Results** Outcome: Local recurrence at median follow up of 55 months, n/total ESD= 0/41 TAR= 5/22 P < 0.01 Outcome: Rectal perforation, n/total ESD= 2/11 TAR= 0/13 Outcome: Subcutaneous emphysema, n/total ESD= 1/11 TAR= 0/13	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Critical risk of bias due to confounding (There is potential for confounding, for example age, but such confounders were not controlled for in the analysis.) Bias in selection of participants into the study: Moderate risk of selection bias (Patient data was collected from a prospective database. The analysis does not account for patient characteristics.) At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
non-invasive rectal tumours **Study dates** January 1998 to December 2006 **Source of funding** Not reported					interventions: Low risk of bias (No cross over between intervention groups) Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Moderate risk of bias (Methods of outcome assessment were comparable between intervention groups. Outcome assessors were aware of the intervention that the participants received.) Bias in selection of the reported result: Low risk of bias **Other information** None
Full citation Lezoche, E., Baldarelli, M., Lezoche, G., Paganini, A. M., Gesuita, R., Guerrieri, M., Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal	**Sample size** n= 100 TME= 50 ELRR= 50 **Characteristics** TME (n=50) Male gender, n (%) 34 (68)	**Interventions** ELRR by TEMS vs laparoscopic TME All patients received neoadjuvant treatment with long-course three-dimensional four-field chemoradiotherapy.	**Details** Randomisation Patients were allocated randomly in equal numbers to the intervention arms by sealed opaque envelopes containing computer generated random numbers.	**Results** Outcome: Overall survival (median follow up 9.6 years); event is death TME= 7/50 ELRR= 10/50 Outcome: Overall survival rate TME= 80% (62 to 90)	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk (random were computer generated) Allocation concealment: unclear risk (not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cancer after neoadjuvant therapy, British Journal of Surgery, 99, 1211-1218, 2012 **Ref Id** 748636 **Country/ies where the study was carried out** Italy **Study type** RCT Follow up study of Lezoche 2005 **Aim of the study** The aim of the study was to assess the oncological results of endoluminal locoregional resection (ELRR) performed via transanal endoscopic microsurgery (TEMS) compared to laparoscopic total mesorectal excision (TME), after neoadjuvant chemoradiotherapy in patients with clinical stage cT2 N0 M0 rectal cancer.	Age, median (IQR)= 66 (60-69) Follow-up, months, median (IQR)= 9.6 (7.4-11.9) Distance of lower tumour margin from anal verge, cm, median (IQR) 5.00 (3-6) ELRR (n=50) Male gender, n (%) 30 (60) Age, median (IQR)= 66 (58-70) Follow-up, years, median (IQR)= 9.6 (8.5-11.1) Distance of lower tumour margin from anal verge, cm, median (IQR) 4.92 (3-6) **Inclusion criteria** ASA fitness grade I–II; superior margin of the tumour located within 6 cm of anal verge; histologically confirmed well (G1) or moderately well (G2) differentiated adenocarcinoma	ELRR= Mucosal incision included all the tattoo spots marked at admission staging, in order to excise a minimum of 1 cm of normal mucosa around the tumour, according to its diameter before neoadjuvant therapy. Starting from the mucosal incision the dissection was continued deeply to remove all the mesorectum adjacent to the tumour, following a cutting line with an angle of approximately 120–135° with respect to the mucosal plane. For posterior and lateral lesions, the deep dissection plane was carried down to the 'holy plane', and for anterior lesions to the level of the vaginal septum or the prostatic capsule. For tumour with a distal limit at the level of the anal canal, the incision included the dentate line and the internal sphincter fibres were partially removed. TME= no description available	Blinding Not blinded Follow-up/outcomes Minimum follow up of 5 years. The primary endpoint of the study was the oncological result in terms of local recurrence or distant metastases. Secondary endpoints were: cancer-related mortality, duration of operation, blood loss, analgesic use, morbidity, hospital stay and 30-day mortality Statistical analysis Continuous data were presented as medians and IQRs. X^2 squared tests and Wilcoxon tests were used to analyse patient demographics and treatments. The probability of failure and survival were estimated using the Kaplan-Meier method and relative risk of complications was calculated with Cox regression models.	ELRR= 72% (51 to 86) p= 0.609 Outcome: Local recurrence TME= 3/50 ELRR= 4/50 Outcome: Disease free survival (median follow up 9.6 years); event is local or distant failure or death TME= 94% (82-98) ELRR= 89% (70-96) p= 0.687 TME=3/50* ELRR= 4/50* Outcome: Mortality (within 30 days), n/total TME= 0/50 ELRR= 0/50 Outcome: Major postoperative complications, n/total TME= 3/50 ELRR= 1/50 *event rate approximated from Kaplan-Meier curve by NGA systematic reviewer	Performance bias Blinding of participants and personnel: high risk (open label) Detection bias Blinding of outcome assessment: unclear risk (not reported, but likely not blinded) Attrition bias Incomplete outcome data: unclear risk (no mention of intention-to-treat approach to analysis. All patients accounted for in follow up). Reporting bias Selective reporting: low risk (primary outcome points were reported) Other bias **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates April 1997 to April 2004 **Source of funding** Not reported	with a diameter no larger than 3 cm. **Exclusion criteria** Higher-risk patients (ASA III–IV) with more proximally located tumours, poorly differentiated (G3) or undifferentiated (G4) tumours, and tumours with lymphovascular or perineural invasion, were excluded				
Full citation Park, S. U., Min, Y. W., Shin, J. U., Choi, J. H., Kim, Y. H., Kim, J. J., Cho, Y. B., Kim, H. C., Yun, S. H., Lee, W. Y., Chun, H. K., Chang, D. K., Endoscopic submucosal dissection or transanal endoscopic microsurgery for nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer, Endoscopy, 44, 1031-1036, 2012 **Ref Id** 749732	**Sample size** N= 63 ESD=30 TEMS=33 **Characteristics** ESD (n=30) Male gender, n (%)= 14 (47) Age, years, mean (SD)= 58.6 (8.3) Follow-up, months, mean (SD)= 20.1 (14.1) Tumour size, mm, mean (SD)= 25.4 (11.0)	**Interventions** ESD vs TEMS ESD= completed with a single-channel colonoscope. Mixture of 10% glycerin, 5% fructose, and 0.9% saline was used as the submucosal injection solution. Indigo carmine and epinephrine were used to identify the muscle and submucosal layers. 2mL of the solution was injected under the tumour until the tumour was lifted and could be resected.	**Details** Randomisation N/A Blinding N/A Follow-up/outcomes Follow up: Colonoscopies were performed every 6 months for 3 years. An abdominal computed tomography scan was performed every 6 months for the first year and then annually to assess distant metastasis.	**Results** Outcome: Local recurrence (median follow up 26 months), n/total ESD= 0/30 TEMS= 0/33 Outcome: Perforation/postoperative leakage, n/total ESD= 1/30 TEMS= 2/33	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias due to confounding (There is potential for confounding, for example type pf anaesthesia or antibiotics, but such confounders were accounted for in the analysis.) Bias in selection of participants into the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out South Korea **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to compare the outcomes of transanal endoscopic microsurgery (TEMS) and endoscopic submucosal dissection (ESD) for the treatment of early rectal cancer. **Study dates** January 2007 to April 2011 **Source of funding** Korea Health 21R&D Project, Ministry of Health and Welfare, Republic of Korea	Location, cm from anal verge, mean (SD)= 10.5 (4.6) TEMS (n=33) Male gender, n (%)= 17 (52) Age, years, mean (SD)= 59.5 (11.0) Follow-up, months, mean (SD)= 27.2 (11.6) Tumour size, mm, mean (SD)= 27.8 (15.0) Location, cm from anal verge, mean (SD)= 6.0 (3.6) p-value location from anal verge < 0.001 **Inclusion criteria** Patients with nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer Had at least 6 months of follow up **Exclusion criteria** case referred because of incomplete resection or indeterminate	TEMS = Patient was under general or spinal anaesthesia. Rectal cavity was insufflated with carbon dioxide to maintain a constant intrarectal pressure. The lesion was magnified and then the cancer was dissected with an en bloc full thickness rectal all excision up to the perirectal fat	Outcomes: En bloc resection rate, R0 resection rate, local recurrence rate, distant metastasis, complications, need for general anaesthesia, need for antibiotics, procedure times and hospital stay Statistical analysis X^2 tests or Fisher's exact tests for categorical variables. Student's t test or Mann-Whitney U test for continuous data. P values were two tailed and 0.05 was considered statistically significant.		study: Low risk of selection bias (No obvious risk of selection bias) At intervention Bias in classification of interventions: Moderate risk of bias (Unclear whether information used to define intervention groups was specified at the start of the intervention. Intervention groups were clearly defined.) Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias due Bias in measurement of outcomes: Low risk of bias (Outcomes were objective and measured by health care professionals, not participant recall)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	pathological results from another hospital Synchronous lesions requiring two sessions of treatment Having co morbid disease that influenced hospital stay Undergoing neoadjuvant chemotherapy				Bias in selection of the reported result: Low risk of bias **Other information** None
Full citation Winde, G., Blasius, G., Herwig, R., Lugering, N., Keller, R., Fischer, R., Benefit in therapy of superficial rectal neoplasms objectivized: Transanal endoscopic microsurgery (TEMS) compared to surgical standards, Minimally Invasive Therapy and Allied Technologies, 6, 315-323, 1997 **Ref Id** 751550 **Country/ies where the study was carried out** Germany	**Sample size** n= 53 AR= 28 TEMS= 25 **Characteristics** AR (n=28) Male gender, n (%)= 15 (54) Age, mean (range)= 60.9 (47-81) Follow up, months, mean (SD)= 45.8 (24.6) TEMS (n=25) Male gender, n (%)= 18 (70) Age, mean (range)= 63.7 (36-90) Follow up, months, mean (SD)= 40.9	**Interventions** Anterior resection (AR) vs TEMS AR: Open laparatomy performed in supine position, dissection along the perirectal fascias, TEMS, ligation of the inferior mesenteric artery and mobilisation of the splenic flexure TEMS: Performed in jack-knife position or in side-positioning. Carcinomas were resected by a full wall thickness excision with a macroscopic circular/lateral 10mm resection margin.	**Details** Randomisation Patients were selected at random using a number table Blinding Not blinded Follow-up/outcomes Follow-up every 3 months for the first 2 years. After 2 years, follow ups every 6 months up to 5 years. Outcomes included: intraoperative blood loss, operation time, time of hospitalisation, early and late morbidity including local and	**Results** Outcome: Overall survival (mean follow up 41 to 46 months); event is death from any cause AR= 1/28 TEMS= 1/25 p= 0.98 HR= 1.02 Outcome: Local recurrence rate, n/total (event is local recurrence) AR= 0/28 TEMS= 1/25 Outcome: Major postoperative complications (ischemic compartment syndrome of the lower leg), n/total AR= 0/28	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: high risk (random numbers table) Allocation concealment: unclear risk (not reported) Performance bias Blinding of participants and personnel: high risk (no blinding) Detection bias Blinding of outcome assessment: unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** The aim of the study was to assess the outcomes of three surgical procedures to cure early rectal cancer. **Study dates** 1984-1992 **Source of funding** Not reported	(24.6) **Inclusion criteria** Low risk rectal cancer with </ 4 cm diameter or sessile rectal adenomas of the lower and middle rectal third TNM stage uT1 negative Tumour location classified to the lower (</= 8cm), middle (>8cm), </=12 cm) and upper (> 12 </= 18cm) rectal third **Exclusion criteria** Not reported		distant recurrence, mortality, post-operative analgesia and survival probability Statistical analysis Kaplan-Meier survival probability, Mantel-Haenszel log rank test, ANOVA, unpaired t-test and one tailed unpaired Wilcoxon rank sum test	TEMS= 1/25 Outcome: Peritoneal perforation, n/total AR= 0/28 TEMS=1/25	(not reported, but likely not blinded) Attrition bias Incomplete outcome data: unclear risk (no mention of intention-to-treat approach to analysis. All patients accounted for in follow up). Reporting bias Selective reporting: low risk (primary outcome points were reported) Other bias: None **Other information** None
Full citation Yan, F. H., Lou, Z., Hu, S. J., Xu, X. D., Wang, H., Wang, H. T., Meng, R. G., Fu, C. G., Zhang, W., He, J., Yu, E. D., Endoscopic submucosal dissection versus transanal local excision for rectal carcinoid: A comparative study, World Journal of Surgical Oncology, 14	**Sample size** N= 54 ESD= 31 TALE= 23 **Characteristics** ESD (n=31) Male gender, n (%)= 22 (71) Age, mean (SD)= 52.2 (10.2)	**Interventions** ESD vs TALE ESD= Patients did not receive anesthesia or IV sedation. Mixture of glycerin, fructose, normal saline, adrenaline, and methlene blue was injected into the submucosal plane. Mucosal incision and	**Details** Randomisation N/A Blinding N/A Follow-up/outcomes Outcomes: operative time, morbidity rate, time to ambulation, hospital stay, bleeding,	**Results** Outcome: Local recurrence, n/total ESD=0/31 TALE= 0/23 Outcome: bleeding or perforation, n/total ESD=0/31 TALE= 0/23	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Critical risk of bias due to confounding (There is potential for confounding, but study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(1) (no pagination), 2016 **Ref Id** 751657 **Country/ies where the study was carried out** China **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to compare the efficacy of two different local excision procedures – transanal local excision (TALE) and endoscopic submucosal dissection (ESD). **Study dates** October 2007 to December 2012 **Source of funding** Changhai Hospital	Follow-up, months, median (IQR)= 16.4 (8-31) Tumour size, cm, mean (SD)= 0.8 (0.2) Distance from anal verge, cm, mean (SD)= 5.9 (2.3) Lymphovascular invasion, n= 0 P value tumour size= 0.018 TALE (n=23) Male gender, n (%)= 14 (61) Age, mean (SD)= 47.9 (11.7) Follow-up, months, median (IQR)= 28.4 (8-68) Tumour size, cm, mean (SD)= 1.1 (0.5) Distance from anal verge, cm, mean (SD)= 5.4 (1.5) Lymphovascular invasion, n= 0 **Inclusion criteria**	submucosal dissection were performed with a needle knife or insulated tip knife. TALE= Patient underwent spinal anesthesia, lithotomy position, or clasp knife position. Anal retractors were used to maintain exposure in the anal canal. Normal saline was injected into the submucosal plane with an injector syringe to create a visible submucosal cushion for elevation of the lesion. Tumour excised with electrocautery or ultrasonic knife.	complication that required re-intervention or resulted in prolonged hospital stay, bleeding, perforation, acute retention of urine. Statistical analysis Fisher exact tests, X^2squared tests, or independent t tests were used to analyse data		was unable to control for confounders.) Bias in selection of participants into the study: Serious risk of selection bias (Although the characteristics of the two groups are reported clearly in the study, the study does not account for any of these characteristics. There was a statistically significant difference between treatment groups in terms of tumour size.) At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias

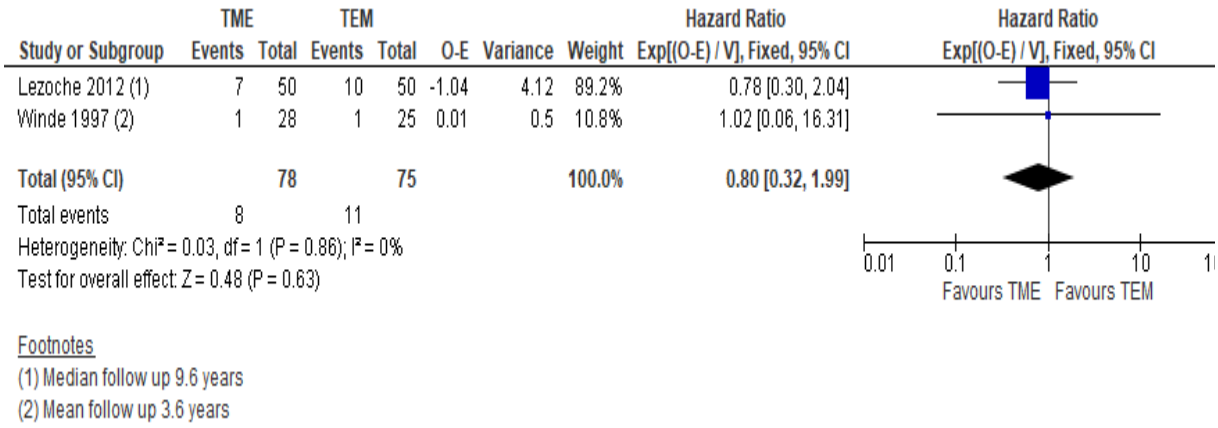
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Tumour located less than 7cm to anal verge Tumour size accounted less than 1/3 lumen diameter TNM staged earlier than T1 **Exclusion criteria** Underwent surgical oncologic resection.				Bias in selection of the reported result: Low risk of bias **Other information** None

AR: anterior resection; ASA: American Society of Anesthesologists; EBRT: external beam radiation therapy; ELRR: endo-luminal locoregional resection; EMR: endomucosal resection; ESD: endoscopic submucosal dissection; EUS: endorectal ultrasound; HR: hazard ratio; IQR: interquartile range; ITT: intention-to-treat; LAR: lower anterior resection; LE: local excision; NGA: National Guideline Alliance; N/A: not applicable; RCT: randomised controlled trial; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions; RR: relative risk; SD: standard deviation; TALE: transanal local excision; TAR: transanal resection; TEMS: transanal endoscopic microsurgery; TME; total mesorectal excision; TNM: cancer classification system, standing for tumour, nodes, metastasis; vs: versus.

Appendix E – Forest plots

Forest plots for review question: What is the most effective treatment for early rectal cancer?

Figure 2: Comparison 1: Total mesorectal excision versus transanal excision – Overall survival (median follow up 9.6 years; mean follow up 3.6 years); event is death from any cause

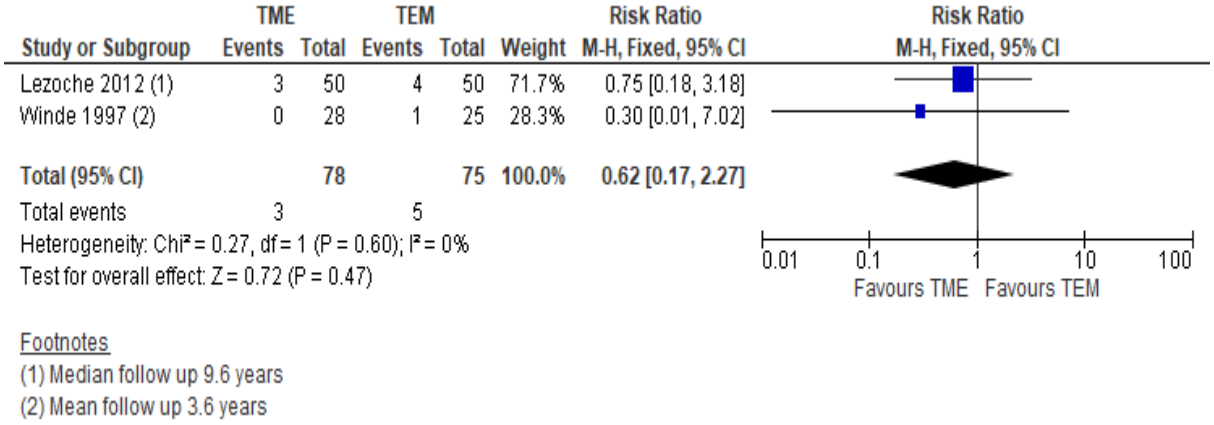


CI: confidence interval; O-E: observed minus expected; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision; V: variance

Figure 3: Comparison 1: Total mesorectal excision versus transanal excision – Local recurrence rate (median follow up 1.5 years); event is local recurrence

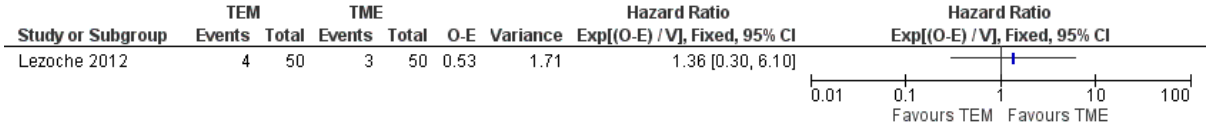
CI: confidence interval; M-H: Mantel-Haenszel; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

Figure 4: Comparison 1: Total mesorectal excision versus transanal excision – Local recurrence rate (median follow up 9.6 years); event is local recurrence



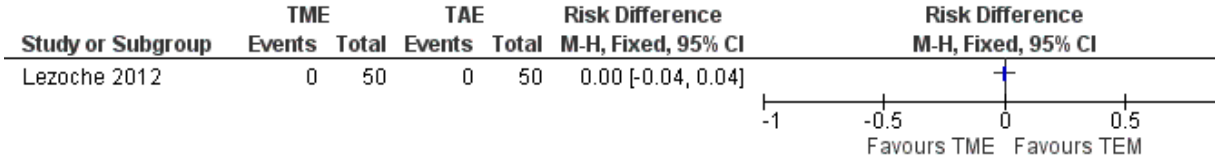
CI: confidence interval; M-H: Mantel-Haenszel; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

Figure 5: Comparison 1: Total mesorectal excision versus transanal excision – Disease free survival (median follow up 9.6 years); event is local or distant failure or death



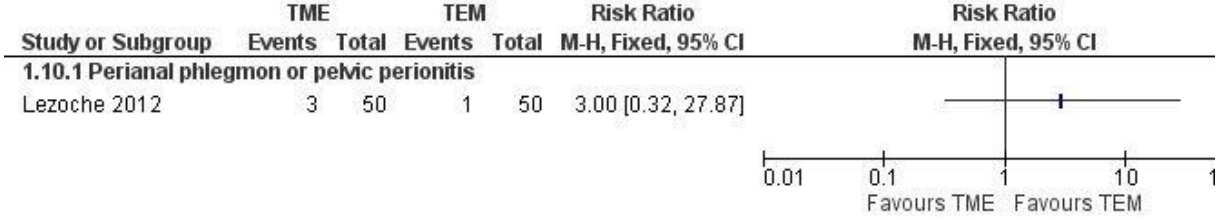
Source: CI: confidence interval; (O-E): observed - expected; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

Figure 6: Comparison 1: Total mesorectal excision versus transanal excision – Mortality within 90 days (timeframe 30 days)



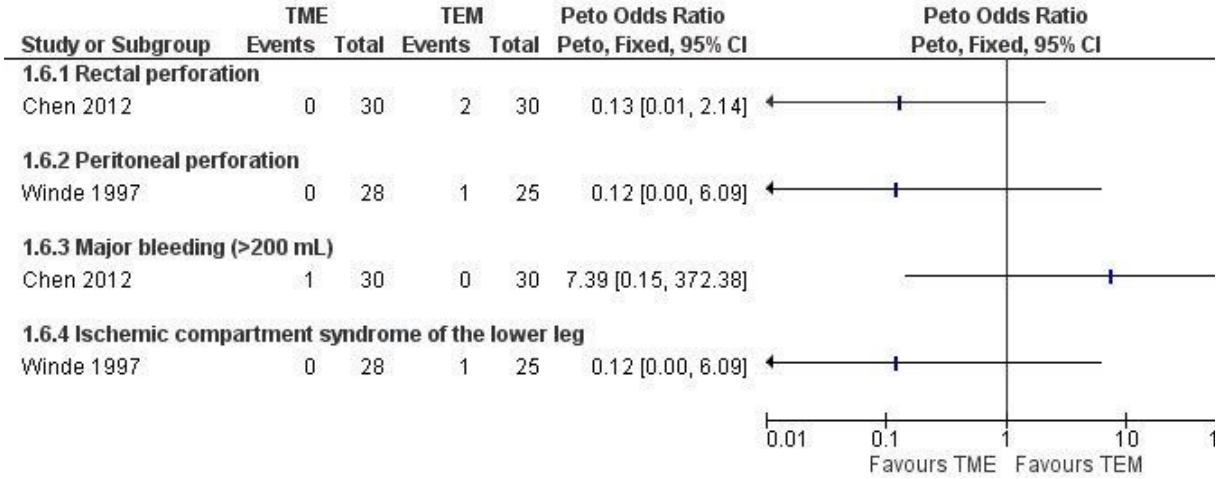
CI: confidence interval; M-H: Mantel-Haenszel; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

Figure 7: Comparison 1: Total mesorectal excision versus transanal excision – Grade 3 or 4 treatment complication (perianal phlegmon or pelvic peritonitis)



CI: confidence interval; M-H: Mantel-Haenszel; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

Figure 8: Comparison 1: Total mesorectal excision versus transanal excision – Grade 3 or 4 treatment complications

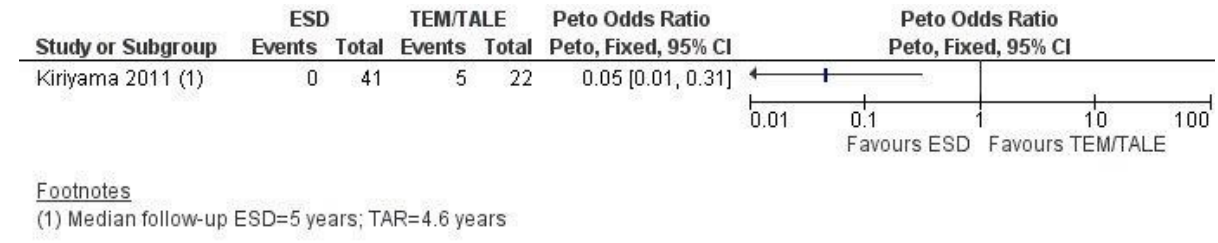


CI: confidence interval; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

Figure 9: Comparison 2: Endoscopic resection versus transanal excision – Local recurrence rate (median follow up 1.3 to 5 years)

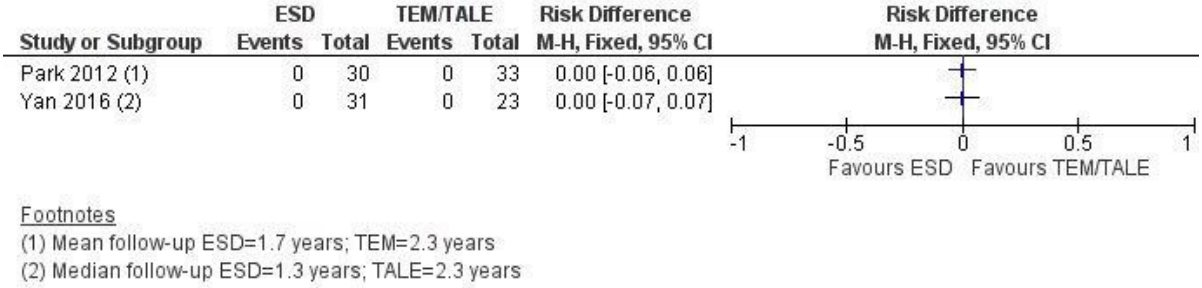
CI: confidence interval; ESD: endoscopic submucosal dissection; TALE: transanal local excision; TEM: transanal endoscopic microsurgery

Figure 10: Comparison 2: Endoscopic resection versus transanal excision – Local recurrence rate (median follow-up 4.6 years)



CI: confidence interval; ESD: endoscopic submucosal dissection; TALE: transanal local excision; TEM: transanal endoscopic microsurgery

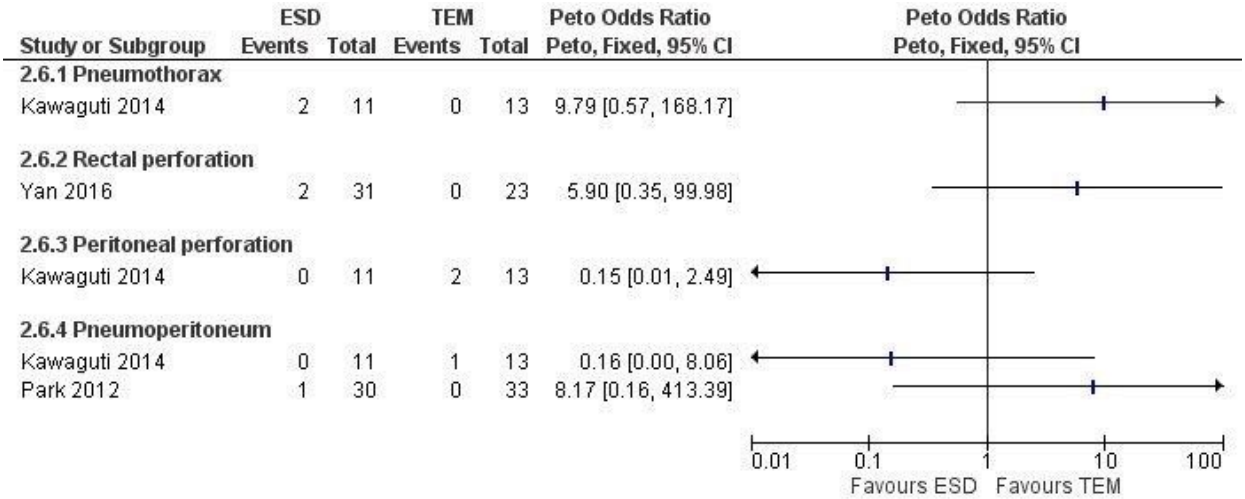
Figure 11: Comparison 2: Endoscopic resection versus transanal excision – Local recurrence rate (median follow-up 1.3 to 2.3 years)



Footnotes
(1) Mean follow-up ESD=1.7 years; TEM=2.3 years
(2) Median follow-up ESD=1.3 years; TALE=2.3 years

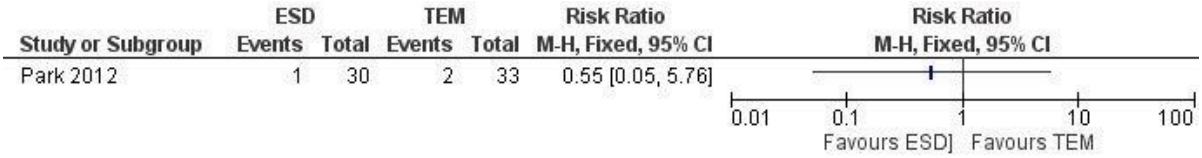
CI: confidence interval; ESD: endoscopic submucosal dissection; M-H: Mantel-Haenszel; TALE: transanal local excision; TEM: transanal endoscopic microsurgery

Figure 12: Comparison 2: Endoscopic resection versus transanal excision – Grade 3 or 4 treatment complications



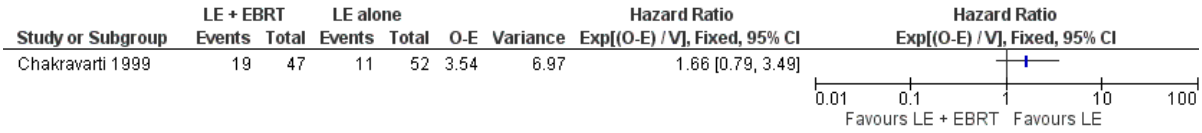
CI: confidence interval; ESD: endoscopic submucosal dissection; TEM: transanal endoscopic microsurgery

Figure 13: Comparison 2: Endoscopic resection versus transanal excision – Grade 3 or 4 treatment complication (perforation/postoperative leakage)



CI: confidence interval; ESD: endoscopic submucosal dissection; M-H: Mantel-Haenszel; TEM: transanal endoscopic microsurgery

Figure 14: Comparison 3: Transanal mesorectal excision versus transanal excision – Local recurrence-free survival (median follow up 4.3 years); event is local recurrence



CI: confidence interval; EBRT: external beam radiotherapy; LE: local excision; O-E: observed minus expected; V: variance

1

2

1 Appendix F – GRADE tables

2 GRADE tables for review question: What is the most effective treatment for early rectal cancer?

3 Table 5: Clinical evidence profile for comparison 1: Total mesorectal excision versus transanal excision

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TME	TAE	Relative (95% CI)	Absolute		
Overall survival (median follow up 9.6 years; mean follow up 3.6 years); event is death from any cause												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/78 (10.3%)	11/75 (14.7%)	HR 0.8 (0.32 to 1.99)	At 9.6 years transanal excision 80%[a], total mesorectal excision 84% (64% to 93%)	LOW	CRITICAL
Overall survival (median follow up 18 months); event is death from any cause												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	0/30 (0%)	Not estimable[c]	Not estimable[c]	LOW	CRITICAL
Local recurrence free survival (median follow up 1.5 years); event is local recurrence												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	2/30 (6.7%)	Peto odds ratio 0.13 (0.01 to 2.14)	At 1.5 years transanal excision 93%[b], total mesorectal excision 99% (81% to 100%)	LOW	CRITICAL
Local recurrence rate (median follow up 9.6 years); event is local recurrence												
2	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	3/78 (3.8%)	5/75 (6.7%)	RR 0.62 (0.17 to 2.27)	25 fewer per 1000 (from 55 fewer to 85 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TME	TAE	Relative (95% CI)	Absolute	Quality	Importance
Overall quality of life (Better indicated by lower values)												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease free survival (median follow up 9.6 years); event is local or distant failure or death												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/50 (8%)	3/50 (6%)	HR 1.36 (0.3 to 6.1)	At 9.6 years transanal excision 94%[a], total mesorectal excision 92% (67% to 98%)	LOW	IMPORTANT
Mortality (within 90 days): 30-days												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	serious[2]	none	0/50 (0%)	0/50 (0%)	RD 0.00 (-0.04, 0.04)	not estimable[5]	LOW	IMPORTANT
Grade 3 or 4 treatment complications - Perianal phlegmon or pelvic perionitis												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	serious[2]	none	3/50 (6%)	1/50 (2%)	RR 3.00 (0.32 to 27.87)	40 more per 1000 (from 14 fewer to 537 more)	LOW	IMPORTANT
Grade 3 or 4 treatment complications - Rectal perforation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	2/30 (6.7%)	Peto odds ratio 0.13 (0.01, 2.14)	57 fewer per 1000 (from 66 fewer to 66 more)	LOW	IMPORTANT
Grade 3 or 4 treatment complications - Peritoneal perforation												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/28 (0%)	1/25 (4%)	Peto odds ratio 0.12 (0.00, 6.09)	35 fewer per 1000 (from 40 fewer to 162 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TME	TAE	Relative (95% CI)	Absolute		
Grade 3 or 4 treatment complications - Major bleeding (> 200 mL)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/30 (3.3%)	0/30 (0%)	Peto odds ratio 7.39 (0.15, 372.38)	109 fewer per 1000 (from 17 fewer to 862 more)	LOW	IMPORTANT
Grade 3 or 4 treatment complications - Ischemic compartment syndrome of the lower leg												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/28 (0%)	1/25 (4%)	Peto odds ratio 0.12 (0.00, 6.09)	35 fewer per 1000 (from 40 fewer to 162 more)	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: relative risk; TAE: transanal excision; TME: total mesorectal excision
1 Quality of the evidence downgraded by 1 because of lack of or unclear allocation and outcome assessment blinding.
2 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).
3 Quality of the evidence was downgraded by 2 because of lack of computer-generated randomisation, and allocation and outcome assessment blinding.
a The absolute risk at 9.6 years in the control group taken from Lezoche 2012.
b The absolute risk at 1.5 years in the control group taken from Chen 2012.
c Not shown in Forest Plot – not estimable

Table 6: Clinical evidence profile for comparison 2: Endoscopic resection versus transanal excision

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic resection	TAE	Relative (95% CI)	Absolute		
Overall survival (follow-up >4 years); event is death from any cause												
1	randomised studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/87 (0%)	0/89 (0%)	not estimable[a]	not estimable[a]	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic resection	TAE	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (median follow up 5 years); event is death from any cause												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/11 (0%)	0/13 (0%)	not estimable[a]	not estimable[a]	VERY LOW	CRITICAL
Overall survival (median follow up 1.6 to 2.4 years); event is death from any cause												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/41 (0%)	0/22 (0%)	not estimable[a]	not estimable[a]	VERY LOW	CRITICAL
Overall survival (median follow up 1.7 to 2.3 years); event is death from any cause												
1	observational studies	No serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	0/33 (0%)	not estimable[a]	not estimable[a]	LOW	CRITICAL
Overall survival (median follow up 1.3 to 2.3 years); event is death from any cause												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/31 (0%)	0/23 (0%)	not estimable[a]	not estimable[a]	VERY LOW	CRITICAL
Local recurrence rate (median follow up 1.3 to 5 years)												
1	randomised studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/87 (15%)	10/89 (11%)	RR 1.33 (0.62, 2.87)	37 more per 1,000 (from 43 fewer to 210 more)	LOW	CRITICAL
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	1/11 (9.1%)	2/13 (15.4 %)	RR 0.59 (0.06 to 5.68)	63 fewer per 1000 (from 145 fewer to 720 more)	VERY LOW	CRITICAL
Local recurrence rate (median follow up 4.6 years)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/41 (0%)	5/22 (22.7 %)	Peto odds ratio 0.05 (0.01, 0.31)	213 fewer per 1,000 (from 224 fewer to 144 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic resection	TAE	Relative (95% CI)	Absolute		
Local recurrence rate (median follow up 1.3 to 2.3 years)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	0/33 (0%)	RD 0.00 (-0.06, 0.06)[a]	not estimable[a]	VERY LOW	CRITICAL
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/31 (0%)	0/23 (0%)	RD 0.00 (-0.07, 0.07)[a]	not estimable[a]	VERY LOW	CRITICAL
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Disease-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Mortality (within 90 days)												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Grade 3 or 4 treatment complications - Pneumothorax												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	2/11 (18.2%)	0/13 (0%)	Peto odds ratio 9.79 (0.57, 168.17)	not estimable[b]	VERY LOW	IMPORTANT
Grade 3 or 4 treatment complications - Rectal perforation												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	2/31 (6.5%)	0/23 (0%)	Peto odds ratio 5.90	not estimable[b]	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic resection	TAE	Relative (95% CI)	Absolute	Quality	Importance
									(0.35, 99.98)			
Grade 3 or 4 treatment complications - Peritoneal perforation												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/11 (0%)	2/13 (15.4 %)	Peto odds ratio 0.15 (0.01, 2.49)	127 fewer per 1000 (from 152 fewer to 158 more)	VERY LOW	IMPORTANT
Grade 3 or 4 treatment complications - Pneumoperitoneum												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/11 (0%)	1/13 (7.7%)	Peto odds ratio 0.16 (0.00, 8.06)	52 fewer per 1000 (from 75 fewer to 592 more)	VERY LOW	IMPORTANT
1	observational studies	no serious risk of bias	no serious inconsistency	serious[4]	serious[2]	none	1/30 (3.3%)	0/33 (0%)	Peto odds ratio 8.17 (0.16, 413.39)	not estimable[b]	VERY LOW	IMPORTANT
Grade 3 or 4 treatment complications - Perforation/postoperative leakage												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[4]	serious[2]	none	1/30 (3.3%)	2/33 (6.1%)	RR 0.55 (0.05 to 5.76)	27 fewer per 1000 (from 58 fewer to 288 more)	VERY LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: relative risk; TAE: transanal excision
1 Quality of the evidence downgraded by 1 because of lack of or unclear allocation and outcome assessment blinding.
2 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).
3 Quality of evidence downgraded by 1 because of lack of controlling for confounders.
4 Quality of evidence downgraded by 1 because a proportion of the people had lymphatic involvement.
a Not estimable due to 0 events in both treatment arms.
b Not estimable due to 0 events in the control arm.

Table 7: Clinical evidence profile for comparison 3: Transanal excision with external radiotherapy or chemoradiotherapy versus transanal excision alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAE with external RT or CRT	TAE alone	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Local recurrence free survival (median follow up 4.3 years); event is local recurrence												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	19/47 (40.4%)	11/52 (21.2 %)	HR 1.66 (0.79 to 3.49)	At 4.3 years transanal excision alone 72%[a], transanal excision with external radiotherapy or chemoradiotherapy 58% (32% to 77%)	VERY LOW	CRITICAL
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Mortality (within 90 days)												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAE with external RT or CRT	TAE alone	Relative (95% CI)	Absolute		
Grade 3 or 4 treatment complications												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; CRT: chemoradiotherapy; HR: hazard ratio; RR: relative risk; RT: radiotherapy; TAE: transanal excision
1 Quality of evidence downgraded by 1 because of lack of controlling for confounders.
2 Quality of evidence downgraded by 1 because a proportion of the people had lymphatic involvement.
a The absolute risk at 9.6 years in the control group taken from Chakravarti 1999.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the most effective treatment for early rectal cancer?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for reviews question: What is the most effective treatment for early rectal cancer?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the most effective treatment for early rectal cancer?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What is the most effective treatment for early rectal cancer?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What is the most effective 3 treatment for early rectal cancer?

4 **Table 8: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Anon. Short-term surgical outcomes and patient quality of life between robotic and laparoscopic extralevator abdominoperineal excision for adenocarcinoma of the rectum. 2017	A conference abstract.
Abdujapparov A, Ten Y, Korakhadjaev B. The results of neoadjuvant chemoradiation therapy in combined treatment of rectal cancer. European Journal of Cancer. 2017;72:S50.	A conference abstract.
Abraha I, Aristei C, Palumbo I, Lupattelli M, Trastulli S, Cirocchi R, et al. Preoperative radiotherapy and curative surgery for the management of localised rectal carcinoma. Cochrane Database Syst Rev. 2018;10:CD002102.	A systematic review and meta-analysis of RCTs comparing preoperative radiotherapy and surgery versus surgery alone. All included studies checked.
Al Bandar, M. H., Han, Y. D., Razvi, S. A., Cho, M. S., Hur, H., Min, B. S., Lee, K. Y., Kim, N. K., Comparison of trans-anal endoscopic operation and trans-anal excision of rectal tumours, Annals of Medicine and Surgery, 14, 18-24, 2017	Intra group comparison - TAE vs TEO
Allaix, M. E., Arezzo, A., Giraudo, G., Morino, M., Transanal Endoscopic Microsurgery vs. Laparoscopic Total Mesorectal Excision for T2N0 Rectal Cancer, Journal of Gastrointestinal Surgery, 16, 2280-2287, 2012	Observational cohort study, no critical outcomes
Benson, A. B., 3rd, New approaches to assessing and treating early-stage colon and rectal cancers: cooperative group strategies for assessing optimal approaches in early-stage disease, Clinical Cancer Research, 13, 6913s-20s, 2007	Systematic review, individual studies checked for inclusion
Bentrem, D. J., Okabe, S., Wong, W. D., Guillem, J. G., Weiser, M. R., Temple, L. K., Ben-Porat, L. S., Minsky, B. D., Cohen, A. M., Paty, P. B., T1 adenocarcinoma of the rectum: transanal excision or radical surgery?, Annals of Surgery, 242, 472-7; discussion 477-9, 2005	Observational cohort study, no critical outcomes
Bernstein, M. A., Amarnath, B., Weiss, E. G., Nogueras, J. J., Wexner, S. D., Total mesorectal excision without adjuvant therapy for local control of rectal cancer: A North American experience, Techniques in Coloproctology, 2, 11-15, 1998	Intra group comparison - low anterior resection vs abdominoperineal resection
Bleday, R., Breen, E., Jessup, J. M., Burgess, A., Sentovich, S. M., Steele, G., Jr., Prospective evaluation of local excision for small rectal cancers, Diseases of the Colon & Rectum, 40, 388-92, 1997	Intra group comparisons - transanal, transphincteric, transcoccygeal excision

Study	Reason for exclusion
Bulow, S., Christensen, I. J., Harling, H., Kronborg, O., Fenger, C., Nielsen, H. J., Danish, T. M. E. Study Group, Ranx Colorectal Cancer Study Group, Recurrence and survival after mesorectal excision for rectal cancer, British Journal of Surgery, 90, 974-80, 2003	Intra-group comparison
Chen K, Xie G, Zhang Q, Shen Y, Zhou T. Comparison of short-course with long-course preoperative neoadjuvant therapy for rectal cancer: A meta-analysis. J Cancer Res Ther. 2018;14(Supplement):S224-S31.	Wrong comparison. (Comparison relevant for review question C2. A systematic review of RCTs)
Chen, R., Liu, X., Sun, S., Wang, S., Ge, N., Wang, G., Guo, J., Comparison of Endoscopic Mucosal Resection with Circumferential Incision and Endoscopic Submucosal Dissection for Rectal Carcinoid Tumour, Surgical Laparoscopy, Endoscopy and Percutaneous Techniques, 26, e56-e61, 2016	Intra group comparison - ESD vs EMR
Chiniah, M., Ganganah, O., Cheng, Y., Sah, S. K., Transanal endoscopic microsurgery is an oncologically safe alternative to total mesorectal excision for stage I rectal cancer: results of a meta-analysis of randomized controlled trials, International Journal of Colorectal DiseaseInt J Colorectal Dis, 31, 1501-1504, 2016	Systematic review, individual studies checked for inclusion
Cho, M. S., Kim, C. W., Baek, S. J., Hur, H., Min, B. S., Baik, S. H., Lee, K. Y., Kim, N. K., Minimally invasive versus open total mesorectal excision for rectal cancer: Long-term results from a case-matched study of 633 patients, Surgery (United States), 157, 1121-1129, 2015	Intra group comparison - robotic TME vs open TME
Choi, C. W., Kang, D. H., Kim, H. W., Park, S. B., Jo, W. S., Song, G. A., Cho, M., Comparison of endoscopic resection therapies for rectal carcinoid tumour: Endoscopic submucosal dissection versus endoscopic mucosal resection using band ligation, Journal of Clinical Gastroenterology, 47, 432-436, 2013	Intra group comparison - ESD vs EMR
Chouillard, E., Regnier, A., Vitte, R. L., Bonnet, B. V., Greco, V., Chahine, E., Daher, R., Biagini, J., Transanal NOTES total mesorectal excision (TME) in patients with rectal cancer: Is anatomy better preserved?, Techniques in Coloproctology, 20, 537-544, 2016	Intra group comparison - Lap-TME vs NOTES-TME
Christoforidis, D., Cho, H. M., Dixon, M. R., Mellgren, A. F., Madoff, R. D., Finne, C. O., Transanal endoscopic microsurgery versus conventional transanal excision for patients with early rectal cancer, Annals of Surgery, 249, 776-782, 2009	Intra group comparison - TAE vs TEMS
Cleary RK, Morris AM, Chang GJ, Halverson AL. Controversies in Surgical Oncology: Does the Minimally Invasive Approach for Rectal Cancer Provide Equivalent Oncologic Outcomes Compared with the Open Approach? Ann Surg Oncol. 2018;25(12):3587-95.	Wrong comparison. (Comparison relevant for review question C3. A systematic review of RCTs and non-RCTs)

Study	Reason for exclusion
Craig-Schapiro, R., Kamel, I. R., Sacerdote, M., Canner, J., Pittman, M., Hicks, C. W., Hacker-Prietz, A., Hobbs, R. F., Armour, E. P., Efron, J. E., Wick, E. C., Azad, N. S., Herman, J. M., Gearhart, S. L., Radiographic predictors of response to endoluminal brachytherapy for the treatment of rectal cancer, Journal of Radiation Oncology, 6, 287-294, 2017	Not early rectal cancer
Cui T, Sun W, He Y, Zhang G, Wang D, Xia Y, et al. The Feasibility and Safety of Interventional Occlusion Treatment of Intracristal Ventricular Septal Defects: Clinical Report of 56 Cases. Cardiology. 2017;137(4):218-24.	Non-randomised study
D'Ambrosio G, Picchetto A, Campo S, Palma R, Panetta C, De Laurentis F, et al. Quality of life in patients with loco-regional rectal cancer after ELRR by TEM versus VLS TME after nChRT: long-term results. Surg Endosc. 2019;33(3):941-8.	No usable data. Data presented graphically but no point estimates reported for the outcomes specified in the scope.
De Graaf, E. J., Doornebosch, P. G., Tollenaar, R. A., Meershoek-Klein Kranenbarg, E., de Boer, A. C., Bekkering, F. C., van de Velde, C. J., Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention, European Journal of Surgical Oncology, 35, 1280-5, 2009	Observational study
Denost Q, Loughlin P, Chevalier R, Celerier B, Didailler R, Rullier E. Transanal versus abdominal low rectal dissection for rectal cancer: long-term results of the Bordeaux' randomized trial. Surg Endosc. 2018;32(3):1486-94.	Wrong comparison. (Comparison relevant for review C3; a non-RCT)
Dhadda, A. S., Martin, A., Killeen, S., Hunter, I. A., Organ Preservation Using Contact Radiotherapy for Early Rectal Cancer: Outcomes of Patients Treated at a Single Centre in the UK, Clinical Oncology, 29, 198-204, 2017	Not comparative
Draeger T, Volkel V, Gerken M, Klinkhammer-Schalke M, Furst A. Long-term oncologic outcomes after laparoscopic versus open rectal cancer resection: a high-quality population-based analysis in a Southern German district. Surg Endosc. 2018;32(10):4096-104.	Wrong comparison. (Comparison relevant for review C3; a non-RCT)
Elmessiry, M. M., Van Koughnett, J. A., Maya, A., DaSilva, G., Wexner, S. D., Bejarano, P., Berho, M., Local excision of T1 and T2 rectal cancer: proceed with caution, Colorectal Disease, 16, 703-9, 2014	Observational cohort study, no critical outcomes
Endreseth, B. H., Myrvold, H. E., Romundstad, P., Hestvik, U. E., Bjerkeset, T., Wibe, A., Transanal excision vs. major surgery for T1 rectal cancer, Diseases of the Colon and Rectum, 48, 1380-1388, 2005	Observational cohort study, no critical outcomes
Feng B, Lu J, Zhang S, Yan X, Li J, Xue P, et al. Laparoscopic abdominoperineal excision with trans-abdominal individualized levator transection: interim analysis of a randomized	Wrong comparison: laparoscopic abdominoperineal resection (LAPR) vs LAPR trans-abdominal individualized levator transection (TILT)

Study	Reason for exclusion
controlled trial. Colorectal Dis. 2017;19(7):O246-O52.	
Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, et al. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Annals of surgery. 2019;269(4):589-95.	Wrong comparison. (Comparison relevant for review C3)
Hallam, S., Messenger, D. E., Thomas, M. G., A Systematic Review of Local Excision after Neoadjuvant Therapy for Rectal Cancer: Are ypT0 Tumours the Limit?, Diseases of the Colon and Rectum, 59, 984-997, 2016	Systematic review, individual studies checked for inclusion
Han, Y., He, Y. G., Lin, M. B., Zhang, Y. J., Yin, L., Jin, X., Li, J. W., Local resection for rectal tumours: Comparative study of transanal endoscopic microsurgery vs. conventional transanal excision the experience in China, Hepato-Gastroenterology, 59, 2490-2493, 2012	Intra group comparison - TAE vs TEM
Heintz, A., Morschel, M., Junginger, T., Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum, Surgical Endoscopy, 12, 1145-8, 1998	Observational cohort study, no critical outcomes
Hida K, Okamura R, Sakai Y, Konishi T, Akagi T, Yamaguchi T, et al. Open versus Laparoscopic Surgery for Advanced Low Rectal Cancer: A Large, Multicenter, Propensity Score Matched Cohort Study in Japan. Annals of surgery. 2018;268(2):318-24.	Wrong comparison. (Comparison relevant for review C3; a non-RCT and data available from RCTs for critical outcomes)
Holmer C, Kreis ME. Systematic review of robotic low anterior resection for rectal cancer. Surg Endosc. 2018;32(2):569-81.	Wrong comparison. (Comparison relevant for review question C3. A systematic review of RCTs and non-RCTs)
Ishikawa, K., Arita, T., Shimoda, K., Hagino, Y., Shiraishi, N., Kitano, S., Usefulness of transanal endoscopic surgery for carcinoid tumour in the upper and middle rectum, Surgical Endoscopy and Other Interventional Techniques, 19, 1151-1154, 2005	Intra group comparison - TAR vs TES
Issa, N., Murninkas, A., Schmilovitz-Weiss, H., Agbarya, A., Powsner, E., Transanal Endoscopic Microsurgery After Neoadjuvant Chemoradiotherapy for Rectal Cancer, Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A, 25, 617-24, 2015	11/13 patients in one treatment are were node-positive or not early rectal cancer
Jimenez-Rodriguez, R., Quezada, F., Lynn, P., Strombon, P., Paty, P. S., Martin, W. R., Garcia Aguilar, J. Similar short-term oncolgical outcomes for robotic and open total mesorectal excision in patients with rectal cancer. 2018 American Society of Colon and Rectal Surgeons Annual Meeting, ASCRS 2018. United States	A conference abstract
Jones K, Qassem MG, Sains P, Baig MK, Sajid MS. Robotic total meso-rectal excision for rectal cancer: A systematic review following the	Wrong comparison. (Comparison relevant for review C3; abstract)

Study	Reason for exclusion
publication of the ROLARR trial. World J Gastrointest Oncol. 2018;10(11):449-64.	
Jung, S. M., Yu, C. S., Park, I. J., Kim, T. W., Kim, J. H., Yoon, Y. S., Lim, S. B., Kim, J. C., Oncologic Safety of Local Excision Compared With Total Mesorectal Excision for ypT0-T1 Rectal Cancer: A Propensity Score Analysis, Medicine, 95, e3718, 2016	Observational cohort study, no critical outcomes
Junginger, T., Goenner, U., Hitzler, M., Trinh, T. T., Heintz, A., Blettner, M., Wollschlaeger, D., Long-term results of transanal endoscopic microsurgery after endoscopic polypectomy of malignant rectal adenoma, Techniques in Coloproctology, 21, 225-232, 2017	Majority of patients had lymphovascular invasion
Junginger, T., Goenner, U., Hitzler, M., Trinh, T. T., Heintz, A., Wollschlaeger, D., Blettner, M., Long-term Oncologic Outcome after Transanal Endoscopic Microsurgery for Rectal Carcinoma, Diseases of the Colon and Rectum, 59, 8-15, 2016	Duplicate
Kidane, B., Chadi, S. A., Kanters, S., Colquhoun, P. H., Ott, M. C., Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: A systematic review and meta-analysis, Diseases of the Colon and Rectum, 58, 122-140, 2015	Systematic review, individual studies checked for inclusion
Kim HJ, Choi GS, Park JS, Park SY, Yang CS, Lee HJ. The impact of robotic surgery on quality of life, urinary and sexual function following total mesorectal excision for rectal cancer: a propensity score-matched analysis with laparoscopic surgery. Colorectal Dis. 2018;20(5):O103-O13.	Wrong comparison. (Comparison relevant for review C3; non-RCT)
Kim MJ, Park SC, Park JW, Chang HJ, Kim DY, Nam BH, et al. Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer: A Phase II Open Label Prospective Randomized Controlled Trial. Annals of surgery. 2018;267(2):243-51.	Wrong comparison. (Comparison relevant for review C3; RCT)
Koedam TWA, Veltcamp Helbach M, Penna M, Wijsmuller A, Doornebosch P, van Westreenen HL, et al. Short-term outcomes of transanal completion total mesorectal excision (cTaTME) for rectal cancer: a case-matched analysis. Surg Endosc. 2019;33(1):103-9.	Wrong comparison: transanal completion total mesorectal excision vs conventional abdominal approach
Lamont, J. P., McCarty, T. M., Digan, R. D., Jacobson, R., Tulanon, P., Lichliter, W. E., Should locally excised T1 rectal cancer receive adjuvant chemoradiation?, American Journal of Surgery, 180, 402-5; discussion 405-6, 2000	Not comparative
Langer, C., Liersch, T., Suss, M., Siemer, A., Markus, P., Ghadimi, B. M., Fuzesi, L., Becker, H., Surgical cure for early rectal carcinoma and large adenoma: Transanal endoscopic microsurgery (using ultrasound or electrosurgery) compared to conventional local	Observational cohort study, no critical outcomes

Study	Reason for exclusion
and radical resection, International Journal of Colorectal Disease, 18, 222-229, 2003	
Law WL, Foo DCC. Comparison of early experience of robotic and transanal total mesorectal excision using propensity score matching. Surg Endosc. 2019;33(3):757-63.	Wrong comparison: transanal completion total mesorectal excision vs robotic surgery; a non-RCT
Le Voyer, T. E., Hoffman, J. P., Cooper, H., Ross, E., Sigurdson, E., Eisenberg, B., Local excision and chemoradiation for low rectal T1 and T2 cancers is an effective treatment, American Surgeon, 65, 625-30; discussion 630-1, 1999	Not comparative
Lebedyev, A., Tulchinsky, H., Rabau, M., Klausner, J. M., Krausz, M., Duek, S. D., Long-term results of local excision for T1 rectal carcinoma: The experience of two colorectal units, Techniques in Coloproctology, 13, 231-236, 2009	Intra group comparison - TAE vs TEM
Lee SH, Kim DH, Lim SW. Robotic versus laparoscopic intersphincteric resection for low rectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis. 2018;33(12):1741-53.	Wrong comparison. (Comparison relevant for review C3; review of RCTs)
Lee, J., Park, H. J., Jung, J. S., The comparison of results between endoscopic submucosal dissection or transanal endoscopic microsurgery for early rectal cancer and rectal subepithelial tumour, Journal of Gastroenterology and Hepatology (Australia), 31, 207, 2016	A conference abstract
Lee, L., Edwards, K., Hunter, I. A., Hartley, J. E., Atallah, S. B., Albert, M. R., Hill, J., Monson, J. R., Quality of Local Excision for Rectal Neoplasms Using Transanal Endoscopic Microsurgery Versus Transanal Minimally Invasive Surgery: A Multi-institutional Matched Analysis, Diseases of the Colon and Rectum, 60, 928-935, 2017	Intra group comparison - TEM vs TAMIS
Lee, W., Lee, D., Choi, S., Chun, H., Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer: Retrospective study, Surgical Endoscopy and Other Interventional Techniques, 17, 1283-1287, 2003	Observational cohort study, no critical outcomes
Levic, K., Bulut, O., Hesselfeldt, P., Bulow, S., The outcome of rectal cancer after early salvage TME following TEM compared with primary TME: A case-matched study, Techniques in Coloproctology, 17, 397-403, 2013	Observational cohort study, no critical outcomes
Lezoche, E., Guerrieri, M., Paganini, A. M., D'Ambrosio, G., Baldarelli, M., Lezoche, G., Feliciotti, F., De Sanctis, A., Transanal endoscopic vs total mesorectal laparoscopic resections of T <inf>2</inf>-N<inf>0</inf> low rectal cancers after neoadjuvant treatment: A prospective randomized trial with a 3-years minimum follow-up period, Surgical Endoscopy and Other Interventional Techniques, 19, 751-756, 2005	Follow up data in Lezoche 2012

Study	Reason for exclusion
Lezoche, G., Baldarelli, M., Mario,, Paganini, A. M., De Sanctis, A., Bartolacci, S., Lezoche, E., A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy, Surgical Endoscopy and Other Interventional Techniques, 22, 352-358, 2008	Follow up data in Lezoche 2012
Li, X., Gui, Y., Han, W., Jiang, H., Qi, D., Yang, Y., Application value of endoscopic submucosal dissection and endoscopic mucosal resection for treatment of rectal carcinoids, Journal of Cancer Research and Therapeutics, 12, C43-C46, 2016	Intra group comparison - ESD vs EMR
Lin Y, Lin H, Xu Z, Zhou S, Chi P. Comparative Outcomes of Preoperative Chemoradiotherapy and Selective Postoperative Chemoradiotherapy in Clinical Stage T3N0 Low and Mid Rectal Cancer. J Invest Surg. 2018:1-9.	Wrong comparison: preoperative chemoradiotherapy vs postoperative radiotherapy; a non-RCT
Lin, G. L., Meng, W. C. S., Lau, P. Y. Y., Qiu, H. Z., Yip, A. W. C., Local resection for early rectal tumours: Comparative study of transanal endoscopic microsurgery (TEM) versus posterior trans-sphincteric approach (Mason's Operation), Asian journal of surgery, 29, 227-232, 2006	Observational cohort study, no critical outcomes
Lu, J. Y., Lin, G. L., Qiu, H. Z., Xiao, Y., Wu, B., Zhou, J. L., Comparison of transanal endoscopic microsurgery and total mesorectal excision in the treatment of T1 rectal cancer: A meta-analysis, PLoS ONE, 10, 1DUMMY, 2015	Systematic review, individual studies checked for inclusion
MacKay, G., Downey, M., Molloy, R. G., O'Dwyer, P. J., Is pre-operative radiotherapy necessary in T<inf>1</inf>-T<inf>3</inf> rectal cancer with TME?, Colorectal Disease, 8, 34-36, 2006	Observational cohort study, no critical outcomes
Marijnen, C. A. M., Nagtegaal, I. D., Kapiteijn, E., Klein Kranenbarg, E., Noordijk, E. M., van Krieken, J. H. J. M., van de Velde, C. J. H., Leer, J. W. H., Radiotherapy does not compensate for positive resection margins in rectal cancer patients: Report of a multicenter randomized trial, International Journal of Radiation Oncology Biology Physics, 55, 1311-1320, 2003	Majority of patients (> 66%) in both arms had TNM stage 3 rectal cancer
Middleton, P. F., Sutherland, L. M., Maddern, G. J., Transanal endoscopic microsurgery: A systematic review, Diseases of the Colon and Rectum, 48, 270-284, 2005	Systematic review, individual studies checked for inclusion
Morino, M., Allaix, M. E., Arolfo, S., Arezzo, A., Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate, Surgical Endoscopy and Other Interventional Techniques, 27, 3315-3321, 2013	Observational cohort study, no critical outcomes
Morino, M., Risio, M., Bach, S., Beets-Tan, R., Bujko, K., Panis, Y., Quirke, P., Rembacken, B., Rullier, E., Saito, Y., Young-Fadok, T., Allaix, M. E., Early rectal cancer: the European Association for Endoscopic Surgery (EAES)	Conference decision paper

Study	Reason for exclusion
clinical consensus conference, Surgical Endoscopy and Other Interventional Techniques, 29, 755-773, 2015	
Morton, D., Magill, L., Handley, K., Brown, G., Ferry, D. R., Gray, Z. B., Quirke, P., Seymour, M. T., Warren, B., Gray, R. G., FOxTROT: Randomized phase II study of neoadjuvant chemotherapy (CT) with or without an anti-EGFR monoclonal antibody for locally advanced, operable colon cancer: Planned interim report, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	Locally advanced cancer
Nash, G. M., Weiser, M. R., Guillem, J. G., Temple, L. K., Shia, J., Gonen, M., Wong, W. D., Paty, P. B., Long-term survival after transanal excision of T1 rectal cancer, Diseases of the Colon and Rectum, 52, 577-582, 2009	Observational cohort study, no critical outcomes
NCT. Laparoscopic Surgery or Robotic-Assisted Laparoscopic Surgery in Treating Patients With Rectal Cancer That Can Be Removed By Surgery. 2010	NCT record, not full text; no results
NCT. Optimisation of Response for Organ Preservation in Rectal Cancer : neoadjuvant Chemotherapy and Radiochemotherapy vs. Radiochemotherapy. 2015	NCT record, not full text; no results
NCT. Phase III Study Comparing Preoperative Chemoradiotherapy Alone Versus Neoadjuvant Chemotherapy With Folfirinox Regimen Followed by Preoperative Chemoradiotherapy for Patients With Resectable Locally Advanced Rectal Cancer. 2013	NCT record, not full text; no results
NCT. Preoperative Chemoradiotheray for Rectal Cancer. 2009	NCT record, not full text; no results
Nienhuser H, Heger P, Schmitz R, Kulu Y, Diener MK, Klose J, et al. Short- and Long-Term Oncological Outcome After Rectal Cancer Surgery: a Systematic Review and Meta-Analysis Comparing Open Versus Laparoscopic Rectal Cancer Surgery. J Gastrointest Surg. 2018;22(8):1418-33.	Wrong comparison. (Comparison relevant for review C3; review of RCTs)
Ohtani H, Maeda K, Nomura S, Shinto O, Mizuyama Y, Nakagawa H, et al. Meta-analysis of Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer. In Vivo. 2018;32(3):611-23.	Wrong comparison. (Comparison relevant for review C3; review of RCTs)
Olsheski, M., Schwartz, D., Rineer, J., Wortham, A., Sura, S., Sugiyama, G., Rotman, M., Schreiber, D., A population-based comparison of overall and disease-specific survival following local excision or abdominoperineal resection for stage i rectal adenocarcinoma, Journal of Gastrointestinal Cancer, 44, 305-312, 2013	Outcomes not relevant
Omidvari, S., Hamedi, S. H., Mohammadianpanah, M., Razzaghi, S., Mosalaei, A., Ahmadloo, N., Ansari, M., Pourahmad, S., Comparison of abdominoperineal resection and low anterior resection in lower and middle rectal cancer,	Intra group comparison - LAR vs abdominoperineal resection

Study	Reason for exclusion
Journal of the Egyptian National Cancer Institute, 25, 151-160, 2013	
Palma, P., Horisberger, K., Joos, A., Rothenhoefer, S., Willeke, F., Post, S., Local excision of early rectal cancer: is transanal endoscopic microsurgery an alternative to radical surgery?, Revista Espanola de Enfermedades Digestivas, 101, 172-8, 2009	Observational cohort study, no critical outcomes
Pappalardo, G., Chiaretti, M., Early rectal cancer: a choice between local excision and transabdominal resection. A review of the literature and current guidelines, Annali Italiani di ChirurgiaAnn Ital Chir, 6, 27, 2017	Systematic review, individual studies checked for inclusion
Paquette, I. M., Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy, Diseases of the Colon and Rectum, 56, e9, 2013	Abstract
Patel, S. A., Chen, Y. H., Hornick, J. L., Catalano, P., Nowak, J. A., Zukerberg, L. R., Bleday, R., Shellito, P. C., Hong, T. S., Mamon, H. J., Early-stage rectal cancer: Clinical and pathologic prognostic markers of time to local recurrence and overall survival after resection, Diseases of the Colon and Rectum, 57, 449-459, 2014	Observational cohort study, no critical outcomes
Peng, J., Chen, W., Venook, A. P., Sheng, W., Xu, Y., Guan, Z., Cai, G., Cai, S., Long-term outcome of early-stage rectal cancer undergoing standard resection and local excision, Clinical Colorectal Cancer, 10, 37-41, 2011	Observational cohort study, no critical outcomes
Prytz M, Ledebo A, Angenete E, Bock D, Haglind E. Association between operative technique and intrusive thoughts on health-related Quality of Life 3 years after APE/ELAPE for rectal cancer: results from a national Swedish cohort with comparison with normative Swedish data. Cancer Med. 2018;7(6):2727-35.	Wrong comparison: APE vs ELAPE (a non-RCT)
Ptok, H., Marusch, F., Meyer, F., Schubert, D., Koeckerling, F., Gastinger, I., Lippert, H., Colon/Rectal Cancer Study, Group, Oncological outcome of local vs radical resection of low-risk pT1 rectal cancer, Archives of Surgery, 142, 649-55; discussion 656, 2007	Observational cohort study, no critical outcomes
Rouanet P, Bertrand MM, Jarlier M, Mourregot A, Traore D, Taoum C, et al. Robotic Versus Laparoscopic Total Mesorectal Excision for Sphincter-Saving Surgery: Results of a Single-Center Series of 400 Consecutive Patients and Perspectives. Ann Surg Oncol. 2018;25(12):3572-9.	Wrong comparison: APE vs ELAPE (a non-RCT)
Rupinski, M., Szczepkowski, M., Malinowska, M., Mroz, A., Pietrzak, L., Wyrwicz, L., Rutkowski, A., Bujko, K., Watch and wait policy after preoperative radiotherapy for rectal cancer; management of residual lesions that appear	Relevant for review C4

Study	Reason for exclusion
clinically benign, European Journal of Surgical Oncology, 42, 288-96, 2016	
Saif, M. W., Hashmi, S., Zelterman, D., Almhanna, K., Kim, R., Capecitabine vs continuous infusion 5-FU in neoadjuvant treatment of rectal cancer. A retrospective review, International Journal of Colorectal Disease, 23, 139-145, 2008	Systematic review, individual studies checked for inclusion
Sajid, M. S., Farag, S., Leung, P., Sains, P., Miles, W. F. A., Baig, M. K., 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 Disease, 16, 2-14, 2014	Systematic review, individual studies checked for inclusion
Serra-Aracil X, Pericay C, Golda T, Mora L, Targarona E, Delgado S, et al. Non-inferiority multicenter prospective randomized controlled study of rectal cancer T2-T3s (superficial) N0, M0 undergoing neoadjuvant treatment and local excision (TEM) vs total mesorectal excision (TME). Int J Colorectal Dis. 2018;33(2):241-9.	Wrong comparison. (Comparison relevant for review C3; a non-RCT)
Seshadri RA, Swaminathan R, Srinivasan A. Laparoscopic versus open surgery for rectal cancer after neoadjuvant chemoradiation: Long-term outcomes of a propensity score matched study. J Surg Oncol. 2018;117(3):506-13.	Wrong comparison. (Comparison relevant for review C3; a study protocol)
Sgourakis, G., Lanitis, S., Gockel, I., Kontovounisios, C., Karaliotas, C., Tsiftsi, K., Tsiamis, A., Karaliotas, C. C., Transanal endoscopic microsurgery for T1 and T2 rectal cancers: A meta-analysis and meta-regression analysis of outcomes, American Surgeon, 77, 761-772, 2011	Systematic review, individual studies checked for inclusion
Short-term surgical outcomes and patient quality of life between robotic and laparoscopic extralevator abdominoperineal excision for adenocarcinoma of the rectum	A conference abstract.
Simillis C, Lal N, Thoukididou SN, Kontovounisios C, Smith JJ, Hompes R, et al. Open Versus Laparoscopic Versus Robotic Versus Transanal Mesorectal Excision for Rectal Cancer: A Systematic Review and Network Meta-analysis. Annals of surgery. 2019.	Wrong comparison. (Comparison relevant for review C3; a non-RCT)
Spiegel DY, Boyer MJ, Hong JC, Williams CD, Kelley MJ, Moore H, et al. Long-term Clinical Outcomes of Nonoperative Management With Chemoradiotherapy for Locally Advanced Rectal Cancer in the Veterans Health Administration. Int J Radiat Oncol Biol Phys. 2019;103(3):565-73.	Wrong comparison. (Comparison relevant for review C2 but a non-RCT)
Stevenson ARL, Solomon MJ, Brown CSB, Lumley JW, Hewett P, Clouston AD, et al. Disease-free Survival and Local Recurrence After Laparoscopic-assisted Resection or Open Resection for Rectal Cancer: The Australasian Laparoscopic Cancer of the Rectum	Wrong comparison. (Comparison relevant for review C2; RCT)

Study	Reason for exclusion
Randomized Clinical Trial. Annals of surgery. 2019;269(4):596-602.	
Stipa, F., Burza, A., Lucandri, G., Ferri, M., Pigazzi, A., Ziparo, V., Casula, G., Stipa, S., Outcomes for early rectal cancer managed with transanal endoscopic microsurgery: A 5-year follow-up study, Surgical Endoscopy and Other Interventional Techniques, 20, 541-545, 2006	Not comparative
Stornes, T., Wibe, A., Nesbakken, A., Myklebust, T. A., Endreseth, B. H., National early rectal cancer treatment revisited, Diseases of the Colon and Rectum, 59, 623-629, 2016	Observational cohort study, no critical outcomes
Takiyama H, Kawai K, Ishihara S, Yasuda K, Otani K, Nishikawa T, et al. Different Impacts of Preoperative Radiotherapy and Chemoradiotherapy on Oncological Outcomes in Patients with Stages II and III Lower Rectal Cancer: A Propensity Score Analysis. Dig Surg. 2018;35(3):212-9.	Wrong comparison: preoperative CRT vs RT
Tarantino, I., Hetzer, F. H., Warschkow, R., Zund, M., Stein, H. J., Zerz, A., Local excision and endoscopic posterior mesorectal resection versus low anterior resection in T1 rectal cancer, British Journal of Surgery, 95, 375-380, 2008	Observational cohort study, no critical outcomes
Tepper, Je, O'Connell, Mj, Petroni, Gr, Hollis, D, Cooke, E, Benson, Ab, Cummings, B, Gunderson, Ll, Macdonald, Js, Martenson, Ja, Adjuvant postoperative fluorouracil-modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: initial results of intergroup 0114, Journal of Clinical Oncology, 15, 2030-2039, 1997	Intra group comparison - combinations of radiotherapy and chemotherapy
Tollenaar, Raem, Kapiteijn, E, Marijnen, Camni, Brinck, M, Steup, WHet al, Total mesorectal exision (TME) with or without preoperative radiotherapy (RT) in the treatment of primary rectal carcinoma, British Journal of Cancer, 85, 5 [abstract no S9], 2001	A conference abstract
Torre, A, García-Berrocal, Mi, Arias, F, Mariño, A, Valcárcel, F, Magallón, R, Regueiro, Ca, Romero, J, Zapata, I, Fuente, C, Fernández-Lizarbe, E, Vergara, G, Belinchón, B, Veiras, M, Molerón, R, Millán, I, Preoperative chemoradiotherapy for rectal cancer: randomized trial comparing oral uracil and tegafur and oral leucovorin vs. intravenous 5-fluorouracil and leucovorin, International journal of radiation oncology, biology, physics, 70, 102-110, 2008	Wrong staging - T3/4
Tytherleigh, M. G., Warren, B. F., Mortensen, N. J., Management of early rectal cancer, British Journal of Surgery, 95, 409-23, 2008	Literature review
Ung, L., Chua, T. C., Engel, A. F., A systematic review of local excision combined with chemoradiotherapy for early rectal cancer, Colorectal Disease, 16, 502-515, 2014	Systematic review, individual studies checked for inclusion

Study	Reason for exclusion
Valenti, V., Hernandez-Lizoain, J. L., Baixauli, J., Pastor, C., Aristu, J., Diaz-Gonzalez, J., Beunza, J. J., Alvarez-Cienfuegos, J. A., Analysis of early postoperative morbidity among patients with rectal cancer treated with and without neoadjuvant chemoradiotherapy, Annals of Surgical Oncology, 14, 1744-51, 2007	Observational cohort study
van den Brink, M., Stiggelbout, A. M., van den Hout, W. B., Kievit, J., Klein Kranenbarg, E., Marijnen, C. A., Nagtegaal, I. D., Rutten, H. J., Wiggers, T., van de Velde, C. J., Clinical nature and prognosis of locally recurrent rectal cancer after total mesorectal excision with or without preoperative radiotherapy, Journal of Clinical Oncology, 22, 3958-64, 2004	Cohort of Dutch TME trial; have RCT evidence for this comparison
van Gijn, W., Marijnen, C. A., Nagtegaal, I. D., Kranenbarg, E. M., Putter, H., Wiggers, T., Rutten, H. J., Pahlman, L., Glimelius, B., van de Velde, C. J., Dutch Colorectal Cancer, Group, Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial, Lancet Oncology, 12, 575-82, 2011	< 2/3 of patients had early rectal cancer (i.e. T1 or T2)
Veerasarn, V., Phromratanapongse, P., Lorvidhaya, V., Lertsanguansinchai, P., Lertbutsayanukul, C., Panichevaluk, A., Boonnuch, W., Chinswangwatanakul, V., Lohsiriwat, D., Rojanasakul, A., Thavichaigarn, P., Jivapaisarnpong, P., Preoperative capecitabine with pelvic radiotherapy for locally advanced rectal cancer (phase I trial), Journal of the Medical Association of Thailand, 89, 1874-84, 2006	Intra-group comparison - APR vs LAR
Veltcamp Helbach M, Koedam TWA, Knol JJ, Velthuis S, Bonjer HJ, Tuynman JB, et al. Quality of life after rectal cancer surgery: differences between laparoscopic and transanal total mesorectal excision. Surg Endosc. 2019;33(1):79-87.	Wrong comparison. (Comparison relevant for review C3; a non-RCT)
Verseveld, M., de Graaf, E. J., Verhoef, C., van Meerten, E., Punt, C. J., de Hingh, I. H., Nagtegaal, I. D., Nuyttens, J. J., Marijnen, C. A., de Wilt, J. H., Carts Study Group, Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study), British Journal of Surgery, 102, 853-60, 2015	Not comparative
Wan, J. F., Yang, L. F., Zhu, J., Li, G. C., Zhang, Z., Adjuvant chemotherapy for patients with ypT0-2N0-category after neoadjuvant chemoradiotherapy for rectal cancer, Molecular and Clinical Oncology, 7, 864-868, 2017	Intra group comparison - different regimens of chemotherapy
Wang F, Fan W, Peng J, Lu Z, Pan Z, Li L, et al. Total mesorectal excision with or without preoperative chemoradiotherapy for resectable mid/low rectal cancer: a long-term analysis of a	Wrong comparison. (Comparison relevant for review C2)

Study	Reason for exclusion
prospective, single-center, randomized trial. Cancer Commun (Lond). 2018;38(1):73.	
Wang X, Zheng B, Lu X, Bai R, Feng L, Wang Q, et al. Preoperative short-course radiotherapy and long-course radiochemotherapy for locally advanced rectal cancer: Meta-analysis with trial sequential analysis of long-term survival data. PLoS One. 2018;13(7):e0200142.	Systematic review, individual studies checked for inclusion
Wang, S., Gao, S., Yang, W., Guo, S., Li, Y., Endoscopic submucosal dissection versus local excision for early rectal cancer: a systematic review and meta-analysis, Techniques in Coloproctology, 20, 1-9, 2016	Systematic review, individual studies checked for inclusion
Wentworth, S., Russell, G. B., Turner, I. I., Levine, E. A., Mishra, G., Waters, G. S., Blackstock, A. W., Long-term results of local excision with and without chemoradiation for adenocarcinoma of the rectum, Clinical Colorectal Cancer, 4, 332-335, 2005	Observational cohort study, no critical outcomes
Wiig, J. N., Larsen, S. G., Dueland, S., Flatmark, K., Giercksky, K. E., Salvage surgery for locally recurrent rectal cancer: Total mesorectal excision during the primary operation does not influence the outcome, Colorectal Disease, 13, 506-511, 2011	Recurrent disease and possibly contains N disease
Willett, C. G., Duda, D. G., Ancukiewicz, M., Shah, M., Czito, B. G., Bentley, R., Poleski, M., Fujita, H., Lauwers, G. Y., Carroll, M., Tyler, D., Mantyh, C., Shellito, P., Chung, D. C., Clark, J. W., Jain, R. K., A safety and survival analysis of neoadjuvant bevacizumab with standard chemoradiation in a phase I/II study compared with standard chemoradiation in locally advanced rectal cancer, Oncologist, 15, 845-51, 2010	Patients had T3/4 rectal cancer
Wiltink, L. M., Chen, T. Y. T., Nout, R. A., Kranenbarg, E. M. K., Fiocco, M., Laurberg, S., Van De Velde, C. J. H., Marijnen, C. A. M., Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomised trial, European Journal of Cancer, 50, 2390-2398, 2014	Results reported in longitudinal study Wiltink 2016
Wiltink, L. M., Marijnen, C. A. M., Kranenbarg, E. M. K., Van De Velde, C. J. H., Nout, R. A., A comprehensive longitudinal overview of health-related quality of life and symptoms after treatment for rectal cancer in the TME trial, Acta Oncologica, 55, 502-508, 2016	Population not relevant - only a proportion of patients had early rectal cancer
Wiltink, Lm, Chen, Tyt, Nout, Ra, Meershoek-Klein, Kranenbarg E, Laurberg, S, Velde, Cjh, Marijnen, Cam, Health-related quality of life of patients 14 years after short-term preoperative radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial, European journal of cancer., 49, S481, 2013	A conference abstract

Study	Reason for exclusion
Wolff, Ha, Liersch, T, Total mesorectal excision with and without preoperative radiotherapy for patients with resectable rectal cancer : the multicentre, randomised controlled TME trial 12-year follow-up, Strahlentherapie und Onkologie, 188, 634-635, 2012	Not in English
Wu QB, Deng XB, Zhang XB, Kong LH, Zhou ZG. & Wang ZQ. Short-Term and Long-Term Outcomes of Laparoscopic Versus Open Surgery for Low Rectal Cancer. J Laparoendosc Adv Surg Tech A, 2018, 28, 637-644.	Wrong comparison (comparison relevant for C3; a non-RCT)
Wu, Aw, Gu, J, Wang, J, Effect of total mesorectal excision and preoperative chemoradiotherapy on local recurrence in rectal cancer, Zhonghua wei chang wai ke za zhi [Chinese journal of gastrointestinal surgery], 9, 207-209, 2006	Full text not in English
Xanthis A, Greenberg D, Jha B, Olafimihan O, Miller R, Fearnhead N, et al. Local recurrence after 'standard' abdominoperineal resection: do we really need ELAPE? Ann R Coll Surg Engl. 2018;100(2):111-5.	No comparator, single arm
Xiao, J., Teng, W. H., Liu, S., Wei, C., Liu, W. J., Chen, S., Zang, W. D. Short-course radiotherapy with delayed surgery versus conventional chemoradiotherapy: Comparison of short-term outcomes in patients with rectal cancer. 2018	Wrong comparison: short course radiotherapy vs CRT
Xu J, Wei Y, Ren L, Feng Q, Chen J, Zhu D, et al. 482PDRobot-assisted vs laparoscopic vs open abdominoperineal resections for low rectal cancer: Short-term outcomes of a single-center prospective randomized controlled trial. Annals of Oncology. 2017;28(suppl_5).	A conference abstract
Yang, D. H., Park, Y., Park, S. H., Kim, K. J., Ye, B. D., Byeon, J. S., Myung, S. J., Yang, S. K., Cap-assisted EMR for rectal neuroendocrine tumours: Comparisons with conventional EMR and endoscopic submucosal dissection (with videos), Gastrointestinal Endoscopy, 83, 1015-1022, 2016	Intra group comparison - EMR vs ESD
You, Y. N., Baxter, N. N., Stewart, A., Nelson, H., Is the increasing rate of local excision for stage I rectal cancer in the United States justified? A nationwide cohort study from the National Cancer Database, Annals of Surgery, 245, 726-733, 2007	Observational cohort study, no critical outcomes
You, Y. N., Baxter, N., Stewart, A., Nelson, H., Is local excision adequate for T1 rectal cancer? A nationwide cohort study from the National Cancer Database (NCDB), Journal of Clinical Oncology, 23, 3526, 2005	A conference abstract
Zhang X, Gao Y, Dai X, Zhang H, Shang Z, Cai X, et al. Short- and long-term outcomes of transanal versus laparoscopic total mesorectal excision for mid-to-low rectal cancer: a meta-analysis. Surg Endosc. 2019;33(3):972-85.	Wrong comparison (Comparison relevant for C3 Systematic review)

Study	Reason for exclusion
Zhang X, Wu Q, Hu T, Gu C, Bi L, Wang Z. Laparoscopic Versus Conventional Open Abdominoperineal Resection for Rectal Cancer: An Updated Systematic Review and Meta-Analysis. J Laparoendosc Adv Surg Tech A. 2018;28(5):526-39.	Full text unobtainable
Zhang, J., Liu, M., Li, H., Chen, J., Su, H., Zheng, J., Lin, G., Lei, X., Comparison of endoscopic therapies for rectal carcinoid tumours: Endoscopic mucosal resection with circumferential incision versus endoscopic submucosal dissection, Clinics and Research in Hepatology and Gastroenterology., 2017	Intra group comparison - EMR vs ESD
Zhang, T., Zhu, J., Chen, J. Y., Zhou, J., Zhu, Y., Jia, J. H., Zhang, C., Wang, X., Gao, Y. H., Cai, G., Luo, B., Wu, J., Liu, A., Xu, B., Zhang, Z., A randomized phase III trial of capecitabine with or without irinotecan driven by UGT1A1 in neoadjuvant chemoradiation of locally advanced rectal cancer (CinClare), Annals of Oncology, 27 (Supplement 9), ix55, 2016	A conference abstract
Zhang, Y., Sun, Y., Xu, Z., Chi, P., Lu, X., Is neoadjuvant chemoradiotherapy always necessary for mid/high local advanced rectal cancer: A comparative analysis after propensity score matching, European Journal of Surgical Oncology, 43, 1440-1446, 2017	Patients did not have early rectal cancer - T3/4, majority N
Zhou, P. H., Yao, L. Q., Qin, X. Y., Xu, M. D., Zhong, Y. S., Chen, W. F., Ma, L. L., Zhang, Y. Q., Qin, W. Z., Cai, M. Y., Ji, Y., Advantages of endoscopic submucosal dissection with needle-knife over endoscopic mucosal resection for small rectal carcinoid tumours: a retrospective study, Surgical EndoscopySurg Endosc, 24, 2607-12, 2010	Intra group comparison - EMR vs ESD
Zhou, X., Xie, H., Xie, L., Li, J., Cao, W., Fu, W., Endoscopic resection therapies for rectal neuroendocrine tumours: A systematic review and meta-analysis, Journal of Gastroenterology and Hepatology (Australia), 29, 259-268, 2014	Intra group comparison - ESD vs EMR
Zhuang, Cp, Li, Th, Wu, Jw, Cai, Gy, Combined preoperative xeloda and radiotherapy for lower rectal cancer, Zhonghua zhong liu za zhi [chinese journal of oncology], 25, 602-603, 2003	Full text not in English

1

Appendix L – Research recommendations

Research recommendations for review question: What is the most effective treatment for early rectal cancer?

No research recommendations were made for this review question.