National Institute for Health and Care Excellence

Draft for consultation

# Colorectal cancer (update)

## [C5] Effectiveness of exenterative surgery for locally advanced or recurrent 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.

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ISBN:

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# Effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer

This evidence review supports recommendation 1.3.10.

## Review question

What is the effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer?

### Introduction

Extensive surgery is often the only method available to achieve local control and potential cure for advanced or recurrent rectal cancer. Pelvic exenteration is a major surgical procedure where all or most organs in the pelvic cavity are removed. However, pelvic exenteration is also associated with high rates of morbidity and changes to quality of life (Ferenschild 2009).

Therefore, the aim of the review is to study the impact that pelvic exenteration has on quality of life, survival, and cancer outcomes among people with locally advanced or locally recurrent rectal cancer. The rate of perioperative complications will also be studied.

### 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 locally advanced or locally recurrent rectal cancer<br><br>Subgroups considered separately:<br>• Locally advanced primary rectal cancer<br>• Locally recurrent rectal cancer |
| **Intervention** | Pelvic exenteration |
| **Comparison** | • Palliative radiotherapy or chemoradiotherapy<br>• Palliative chemotherapy<br>• Supportive care |
| **Outcomes** | **Critical**<br>• Quality of life<br>  ○ Overall<br>  ○ Urological<br>  ○ Gastrointestinal<br>  ○ Sexual<br>• Overall survival<br>• Local recurrence<br><br>**Important** |

| | |
|---|---|
| | • Distant metastasis<br>• Disease-free survival<br>• Perioperative mortality<br>• Perioperative complications<br>  ○ Surgical site infection<br>  ○ Blood loss<br>  ○ Venous thromboembolism |

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

One cohort study (N=117) was included in this review (Choy 2017).

The included study is summarised in Table 2.

The study compared pelvic exenteration to non-exenterative treatment, which included chemotherapy, radiotherapy, chemotherapy + radiotherapy or palliative surgery.

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 study that was included in this review is presented in Table 2.

**Table 2: Summary of included study**

| Study | Population | Intervention/Comparison | Outcomes |
|---|---|---|---|
| Choy 2017<br><br>Prospective cohort study<br><br>Australia | N=117 patients with recurrent rectal cancer referred for pelvic exenteration surgery | Pelvic exenteration versus non-exenterative treatments (including chemotherapy, radiotherapy, chemotherapy + radiotherapy or palliative | • Quality of life<br>• Operative mortality<br>• Perioperative complications |

| Study | Population | Intervention/Comparison | Outcomes |
|---|---|---|---|
| | | surgery excluding exenteration) | |

*N: number*

## Quality assessment of clinical outcomes included in the evidence review

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

## 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: Pelvic exenteration versus non-exenterative treatments***

#### Critical outcomes

#### Quality of life

- Very low quality evidence from 1 prospective cohort study (N=117) showed no clinically important difference in quality of life (measured using AQoL scale) at 12 months between those receiving pelvic exenteration compared to those receiving non-exenterative treatments.
- Very low quality evidence from 1 prospective cohort study (N=117) showed no clinically important difference in quality of life (measured using SF-6D scale) at 12 months between those receiving pelvic exenteration compared to those receiving non-exenterative treatments.

#### Overall survival

No evidence was identified to inform this outcome.

#### Local recurrence

No evidence was identified to inform this outcome.

### Important outcomes

#### Distant metastases

No evidence was identified to inform this outcome.

#### Disease-free survival

No evidence was identified to inform this outcome.

#### Perioperative mortality

- Very low quality evidence from 1 prospective cohort study (N=117) showed no clinically important difference in 30-day mortality between receiving pelvic exenteration compared to non-exenterative treatments.
- Very low quality evidence from 1 prospective cohort study (N=117) showed a clinically significant decrease in 12-month mortality between receiving pelvic exenteration compared to non-exenterative treatments.

#### Perioperative complications

- Very low quality evidence from 1 prospective cohort study (N=117) showed a clinically significant increase in perioperative complications between receiving pelvic exenteration compared to non-exenterative treatments.

### 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*

Quality of life was a critical outcome because of the impact that such a complex and invasive procedure as pelvic exenteration can have on patients' functioning and the potential long term adverse effects. Overall survival and local recurrence were also considered critical outcomes for decision making because local recurrence suggests ineffective treatment of the locally advanced or locally recurrent rectal cancer, potentially requiring further treatment and affecting overall survival. Local recurrence can also cause potentially devastating symptoms.

Distant metastasis and disease-free survival were important outcomes because they suggest ineffective control of the locally advanced or locally recurrent disease. Additionally, perioperative mortality and perioperative complications were also important outcomes, as they are indicative of the short-term side effects of treatments.

#### *The quality of the evidence*

Evidence was available from one study that compared pelvic exenteration to non-exenterative treatments, which included radiotherapy, chemotherapy, radiotherapy plus chemotherapy or palliative surgery. Evidence was available for quality of life, perioperative mortality and perioperative complications. There was no evidence for overall survival beyond 12 months, local recurrence, distant metastases or disease-free survival.

The quality of the evidence was assessed using GRADE and was of very low quality.

The quality of evidence was 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 patients self-selecting into treatment groups and the subjective nature of some of the outcomes, as well as the study not reporting all of the outcomes that were listed in as outcomes of the study.

Indirectness of the study population was attributable to a proportion of the control group receiving palliative surgery (colostomy, ileostomy closure and local excision).

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes.

***Benefits and harms***

The committee agreed that the evidence was limited and of poor quality. However, based on the limited evidence and their clinical expertise, the committee decided to recommend considering referring people with locally advanced recurrent rectal cancer to specialist centres to discuss exenterative surgery. Exenterative surgery is complex and complicated, therefore, a specialist centre is required to perform the surgery. The option of pelvic exenteration may be suitable for those people with locally advanced or recurrent rectal cancer who might potentially need multi-visceral or beyond-TME surgery, meaning more extensive surgery than the standard TME.

The committee noted that with more people being referred to specialist centres to discuss the option of exenterative surgery, more people will be considered for potentially curative surgery who may have otherwise only have received palliative treatments. However, pelvic exenteration is complex and invasive surgery that is often accompanied by changes to lifestyle, notably, postoperative complications, the possibility of two stomas and subsequent changes to quality of life. Due to the severity of the side effects of exenteration, it is crucial that patients are aware of these potential complications and issues before proceeding with surgery.

Despite the lack of evidence the committee did not make a research recommendation because a prospective comparative study would not be feasible due to the low number of eligible participants. They also acknowledged that an international collaborative study of outcomes after pelvic exenteration (PelvEx) is already underway.

**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 may increase the number of referrals to specialist centres and therefore may also increase the number of exenteration procedures. The committee highlighted that pelvic exenteration is an expensive operation due to several factors including prolonged surgical and recovery time and length of hospital stay. However, pelvic exenteration can potentially increase survival for patients with locally advanced or recurrent rectal cancer and so may be a cost effective of resources. Given the significant associated morbidities it is likely that only some of this patient group would opt for such a procedure. While there is a potential cost impact associated with the

recommendations, given the more expensive interventions only impact upon a small proportion of the patient group, it is not expected to be significant.

### Other factors the committee took into account

Data from the PelvEx Collaborative's international collaboration assessing patient outcomes after pelvic exenteration (PelvEx 2017; PelvEx 2018) were not included in the analysis of this review because the data was not comparative. However, the committee discussed the study's results due to their value in demonstrating the effect of exenteration on survival outcomes. For 1291 patients with locally advanced primary rectal cancer who had pelvic exenteration, negative resection margins (R0) were achieved in 79.9% of patients, 30-day post-operative mortality was 1.5%, and median overall survival and 3-year overall survival following R0 resections was 43 months and 56.4%, respectively (PelvEx 2017). For 1184 patients with locally recurrent rectal cancer, negative resection margins were achieved in 55.4% of patients, 30-day post-operative mortality was 1.8%, and median overall survival and 3-year overall survival following R0 resections were 36 months and 48.1%, respectively (PelvEx 2018).

The committee recognised that there may barriers to access specialist centres for some people far away from these centres due to the distance and because of difficulty or cost of transport. The option of receiving treatment in a centre far away from home and family members could impact the decision that a patient makes about their care. Barriers to care in specialist centres for those living far away from these centres could be alleviated by ensuring transport is available to those who require assistance and suitable hostel type accommodation for relatives and carers is made available at major referral sites when daily visiting is not realistic because of the distance.

## References

**Austin 2009**

Austin K and Solomon M (2009) Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. Diseases of the Colon and Rectum 52(7): 1223-1233

**Choy 2017**

Choy I, Young J, Badgery-Parker T, et al. (2017) Baseline quality of life predicts pelvic exenteration outcome. Australian and New Zealand Journal of Surgery, 87(11): 935-939

**Ferenschild 2009**

Ferenschild F, Vermaas M, Verhoef C, et al. (2009) Total pelvic exenteration for primary and recurrent malignancies. World Journal of Surgery 33(7): 1502-1508

**Leppink 2017**

Leppink J, O'sullivan P and Winston K, (2017) Are differences between groups different at different occasions? Perspectives on Medical Education 6(6): 413-417

**PelvEx 2017**

PelvEx Collaborative (2019) Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer: Results from an International Collaboration. Annals of Surgery 09(21)

**PelvEx 2018**

PelvEx Collaborative (2018) Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. British Journal of Surgery 105(6) 650-657

**Young 2014**

Young J, Badgery-Parker T, Masya L, et al. (2014) Quality of life and other patient-reported outcomes following exenteration for pelvic malignancy. British Journal of Surgery 101(3): 277-287

# Appendices

## Appendix A – Review protocol

### Review protocol for review question: What is the effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer?

**Table 3: Review protocol for effectiveness of exenteration for locally advanced or recurrent rectal cancer**

| Field (based on PRISMA-P) | Content |
|---|---|
| Review question in guideline | What is the effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer? |
| Type of review question | Intervention |
| Objective of the review | Pelvic exenteration is a major surgical procedure where all or most organs in the pelvic cavity are removed and it is sometimes used to treat locally advanced or locally recurrent rectal cancer which is not treatable with less radical treatments.<br>The aim of the review is to study the impact that pelvic exenteration has on the quality of life, survival, and cancer among people with locally advanced or locally recurrent rectal cancer. The rate of perioperative complications will also be studied. |
| Eligibility criteria – population/disease/condition/issue/domain | Adults with locally advanced or locally recurrent rectal cancer.<br><br>Rectal cancer defined as any tumour within 15cm from the anal verge excluding the anal canal.<br><br>Subgroups considered separately:<br>• Locally advanced primary rectal cancer<br>• Locally recurrent rectal cancer |
| Eligibility criteria – intervention(s)/exposure(s)/ prognostic factor(s) | Pelvic exenteration |
| Eligibility criteria – comparator(s)/control or reference (gold) standard | • Palliative radiotherapy or chemoradiotherapy<br>• Palliative chemotherapy<br>• Supportive care |
| Outcomes and prioritisation | **Critical outcomes:**<br>• Quality of life measured using validated scales (minimally important difference [MID]: from literature, see below):<br>  ○ Overall<br>  ○ Urological<br>  ○ Gastrointestinal<br>  ○ Sexual<br>• Overall survival (MID: statistical significance)<br>• Local recurrence (MID: statistical significance)<br><br>**Important outcomes:** |

| Field (based on PRISMA-P) | Content |
|---|---|
| | • Distant metastasis (MID: statistical significance)<br>• Disease-free survival (MID: statistical significance)<br>• Perioperative mortality (MID: statistical significance)<br>• Perioperative complications (only applicable for pelvic exenteration arm):<br>  ○ Surgical site infection<br>  ○ Blood loss<br>  ○ Venous thromboembolism<br><br>Quality of life MIDs from the literature:<br>• EORTC QLQ-C30: 5 points*<br>• EORTC QLQ-CR29: 5 points*<br>• EORTC QLQ-CR38: 5 points*<br>• EQ-5D: 0.09 using FACT-G quintiles<br>• FACT-C: 5 points*<br>• FACT-G: 5 points*<br>• SF-12: > 3.77 for the mental component summary (MCS) and > 3.29 for the physical component summary (PCS) of the Short Form SF-12 (SF-12)<br>• SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary<br><br>*Confirmed with guideline committee. |
| Eligibility criteria – study design | • Systematic reviews of randomised controlled trials (RCTs) or non-randomised studies<br>• RCTs<br>• Prospective or retrospective cohort of case-control studies<br><br>Case reports will not be considered. |
| Other inclusion exclusion criteria | Inclusion:<br>• English-language<br>• All settings will be considered that consider medications and treatments available in the UK<br>• Studies published in full text from year 2000 onwards<br><br>Studies published post 2000 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 2000 would not be relevant any longer. |
| Proposed sensitivity/sub-group analysis, or meta-regression | In non-randomised studies, multivariate analysis should be done adjusting for potential confounders or case mix, for example:<br>• Locally advanced primary rectal cancer or locally recurrent rectal cancer<br>• Lymphatic invasion on final pathology<br>• Neoadjuvant therapy given |

| Field (based on PRISMA-P) | Content |
|---|---|
| | • Adjuvant therapy given<br>• 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.<br><br>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).<br><br>'GRADEpro' will be used to assess the quality of evidence for each outcome.<br><br>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 Information Scientist): Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase<br>Limits (e.g. date, study design):<br>Apply standard animal/non-English language exclusion<br>Limit to RCTs and systematic reviews in first instance, but download all results<br>Dates: from 2000<br><br>Existing systematic reviews:<br><br>Rausa E, Kelly ME, Bonavina L, O'Connell PR, Winter DC. A systematic review examining quality of life following pelvic exenteration for locally advanced and recurrent rectal cancer. Colorectal Dis. 2017 May;19(5):430-436. doi: 10.1111/codi.13647.<br><br>Yang TX1, Morris DL, Chua TC. Pelvic exenteration for rectal cancer: a systematic review. Dis Colon Rectum. 2013 Apr;56(4):519-31. doi: 10.1097/DCR.0b013e31827a7868.<br><br>Sasikumar A, Bhan C, Jenkins JT, Antoniou A, Murphy J. Systematic Review of Pelvic Exenteration With En Bloc Sacrectomy for Recurrent Rectal Adenocarcinoma: R0 Resection Predicts Disease-free Survival. Dis Colon Rectum. 2017 Mar;60(3):346-352. doi: 10.1097/DCR.0000000000000737. |
| Identify if an update | Not an update |

| Field (based on PRISMA-P) | Content |
|---|---|
| Author contacts | https://www.nice.org.uk/guidance/indevelopment/gid-ng10060<br>Developer: NGA |
| Highlight if amendment to previous protocol | Not an update |
| 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). |
| 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<br><br>Appraisal of methodological quality:<br>The methodological quality of each study will be assessed using an appropriate checklist:<br>• ROBIS for systematic reviews<br>• Cochrane risk of bias tool for RCTs<br>• ROBINS-I for non-randomised studies<br>The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE.<br><br>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:<br>Pairwise meta-analysis of randomised trials will be conducted where appropriate.<br><br>Data from non-randomised studies will not pooled but will be reported individually and as ranges. Data from RCTs and data from non-randomised studies will not be pooled.<br><br>When meta-analysing continuous data from RCTs, 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.<br><br>Minimally important differences:<br>The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except for quality of life for which published |

| Field (based on PRISMA-P) | Content |
|---|---|
| | 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.<br>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.<br>Staff from The NGA 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. |
| 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 |

*CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; SD: standard deviation*

# 1 Appendix B – Literature search strategies

## 2 Literature search strategies for review question: What is the effectiveness of 3 exenteration for locally advanced or recurrent rectal cancer?

### 4 Databases: Embase/Medline

5 Last searched on: 15/02/2019

| # | Search |
|---|---|
| 1 | (exp colorectal cancer/ or exp colon tumor/ or exp rectum cancer/ or exp rectum tumor/ or exp rectum carcinoma/) use emez |
| 2 | (exp rectal neoplasms/ or exp colorectal neoplasms/) use ppez |
| 3 | ((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw. |
| 4 | or/1-3 |
| 5 | pelvis exenteration/ use emez |
| 6 | Pelvic exenteration/ use ppez |
| 7 | exenterat*.tw. |
| 8 | Evisceration/ use emez |
| 9 | eviscerat*.tw. |
| 10 | ((Abdominosacral or abdomin* sacral) adj3 resect*).tw. |
| 11 | (multiviscer* adj3 resect*).tw. |
| 12 | ((Sacropelvic or sacral) adj3 resect*).tw. |
| 13 | sacrectom*.tw. |
| 14 | (pelvic adj3 resect*).tw. |
| 15 | radical resect*.tw. |
| 16 | or/5-15 |
| 17 | 4 and 16 |
| 18 | limit 17 to english language |
| 19 | limit 18 to yr="2000 - current" |
| 20 | remove duplicates from 19 |
| 21 | Letter/ use ppez |
| 22 | letter.pt. or letter/ use emez |
| 23 | note.pt. |
| 24 | editorial.pt. |
| 25 | Editorial/ use ppez |
| 26 | News/ use ppez |
| 27 | exp Historical Article/ use ppez |
| 28 | Anecdotes as Topic/ use ppez |
| 29 | Comment/ use ppez |
| 30 | Case Report/ use ppez |
| 31 | case report/ or case study/ use emez |
| 32 | (letter or comment*).ti. |
| 33 | or/21-32 |
| 34 | randomized controlled trial/ use ppez |
| 35 | randomized controlled trial/ use emez |
| 36 | random*.ti,ab. |
| 37 | or/34-36 |
| 38 | 33 not 37 |
| 39 | animals/ not humans/ use ppez |
| 40 | animal/ not human/ use emez |
| 41 | nonhuman/ use emez |

| # | Search |
|---|---|
| 42 | exp Animals, Laboratory/ use ppez |
| 43 | exp Animal Experimentation/ use ppez |
| 44 | exp Animal Experiment/ use emez |
| 45 | exp Experimental Animal/ use emez |
| 46 | exp Models, Animal/ use ppez |
| 47 | animal model/ use emez |
| 48 | exp Rodentia/ use ppez |
| 49 | exp Rodent/ use emez |
| 50 | (rat or rats or mouse or mice).ti. |
| 51 | or/38-50 |
| 52 | 20 not 51 |

1 **Database: Cochrane Library**

2 Last searched on: 15/02/2019

| # | Search |
|---|---|
| 1 | MeSH descriptor: [Rectal Neoplasms] explode all trees |
| 2 | ((rectal or rectum) near (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)) |
| 3 | #1 or #2 |
| 4 | MeSH descriptor: [Pelvic Exenteration] explode all trees |
| 5 | exenterat* |
| 6 | eviscerat* |
| 7 | ((Abdominosacral or abdomin* sacral) near resect*) |
| 8 | (multiviscer* near resect*) |
| 9 | ((Sacropelvic or sacral) near resect*) |
| 10 | sacrectom* |
| 11 | (pelvic near resect*) |
| 12 | radical resect* |
| 13 | {or #4-#12} |
| 14 | #3 and #13 Publication Year from 2000 to 2018 |

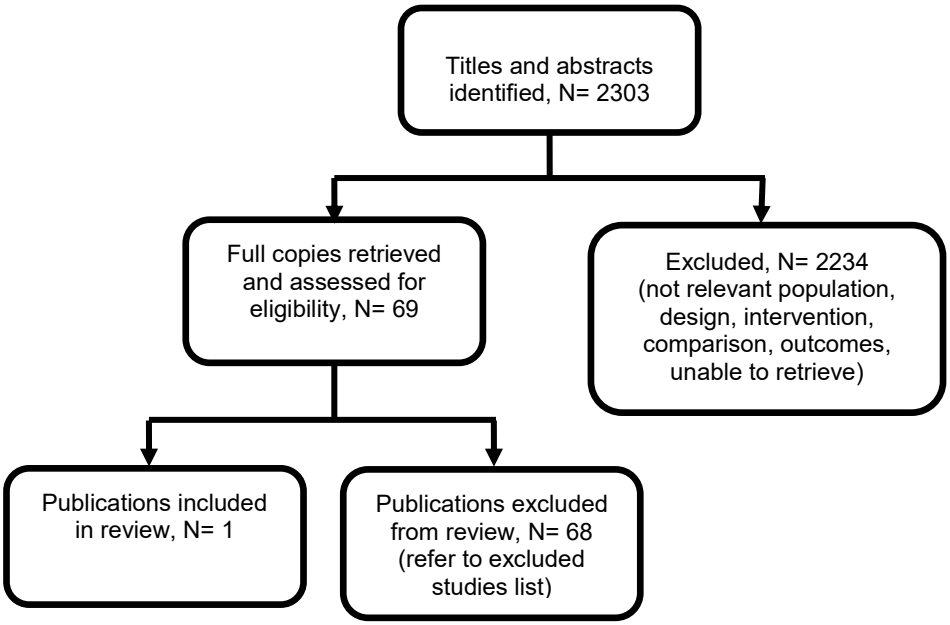
3

4

# Appendix C – Clinical evidence study selection

## Clinical study selection for review question: What is the effectiveness of exenteration for locally advanced or recurrent rectal cancer?

**Figure 1: Study selection flow chart**



# Appendix D – Clinical evidence tables

## Clinical evidence tables for review question: What is the effectiveness of exenteration for locally advanced or recurrent rectal cancer?

**Table 4: Clinical evidence tables for the effectiveness of exenteration for locally advanced or recurrent rectal cancer**

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| **Full citation**<br><br>Choy, I., Young, J. M., Badgery-Parker, T., Masya, L. M., Shepherd, H. L., Koh, C., Heriot, A. G., Solomon, M. J., Baseline quality of life predicts pelvic exenteration outcome, ANZ journal of surgery, 87, 935-939, 2017<br><br>**Ref Id**<br><br>760577<br><br>**Country/ies where the study was carried out**<br><br>Australia<br><br>**Study type**<br>Prospective cohort study<br><br>**Aim of the study**<br>The aim of the study was to assess patients' quality of life 12 months after pelvic exenteration | **Sample size**<br>n= 117<br>n PE= 93<br>n non-PE= 24<br><br>**Characteristics**<br>PE, n= 93<br>Age, years, median= 61<br>Male, n= 64<br>ASA score, n (19 missing values)<br>1= 9<br>2= 45<br>3= 20<br>Any bony resection (1 value missing), n= 62<br>Excision major sacral nerve, n= 40<br>Complete R(0) resection margins (8 missing values), n= 68<br>2 anatomical compartments involved, n= 16 | **Interventions**<br>Description of intervention from Young 2014: Patients who were deemed suitable and agreed to proceed with radical surgery underwent pelvic exenteration using previously reported surgical protocols. That is, e*n bloc* lateral pelvic wall dissection and vascular resection with pelvic exenteration (Austin 2009)<br>Patients in the control group were those who did not proceed with PE, those with localised technical features such that achievement of an R0 resection was unlikely or who received other types of palliative surgical procedure, but they did not undergo pelvic exenteration. | **Details**<br>Data collection: The authors used data from patients with recurrent rectal cancer from the Young 2014 study and added patients recruited up to April 2013. QoL was assessed using a suite of instruments including the FACT-C, which assesses QoL aspects specific to colorectal cancer, and two generic QoL measures, the Assessment of Quality of Life (AQOL) and the SF6D. The AQOL is a multi-attribute utility instrument designed for the evaluation of public health and acute care whereas the SF6D is a utility scale calculated from the SF36v2. On enrolment to the study (baseline), just before hospital discharge (pelvic exenteration group only) and then at 1, 3, 6, 9 and 12 months, patients in both groups completed self-administered questionnaires to assess quality of life and other patient-reported outcomes.<br>Confounders: Age, sex, baseline QoL score, R0 margins, ASA score, extent of surgery, bone resection, excision of the major sacral nerve | **Results**<br>AQOL, median (IQR), n<br>PE baseline= 0.68 (0.49-0.84), 80<br>PE 12 months= 0.48 (0.07-0.73), 77<br>Non-PE baseline= 0.55 (0.29-0.80), 21<br>Non-PE 12 months= 0.14 (0.00-0.54), 21<br>('The trajectories are different between the groups (group x time interaction p= 0.04), but there is no significant difference at any one time point)<br>SF6D, median (IQR), n<br>PE baseline= 0.62 (0.56-0.74), 78<br>PE 12 months= 0.58 (0.33-0.68), 71<br>Non-PE baseline= 0.61 (0.56-0.74), 21<br>Non-PE 12 months= 0.53 (0.00-0.62), 18<br>(group x time interaction statistically significant, but no | **Limitations**<br>ROBINS-I checklist for non-randomised studies of interventions<br>Pre-intervention<br>Bias due to confounding: High risk of bias due to confounding (High potential for confounding, study did not assess differences in baseline characteristics; patients in non-PE group likely to be sicker if surgery unlikely to be non-curative)<br>Bias in selection of participants into the study: Serious risk of selection bias (Patients self-selected into PE or non-PE group)<br>At intervention<br>Bias in classification of interventions: Low risk<br>Post-intervention<br>Bias due to deviations from intended interventions: Low risk of bias<br>Bias due to missing data: Moderate risk of bias |

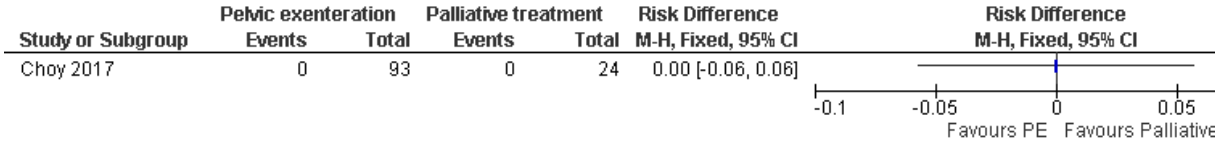
| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| **Study dates**<br>May 2008 to April 2013<br><br>**Source of funding**<br>Cancer Australia and the Cancer Council Australia through the Priority-driven Collaborative Cancer Research Scheme (PdCCRS). Professor Young is supported by the Cancer Institute NSW through an Academic Leader in Cancer Epidemiology grant (08-EPC_1-01). Dr Cherry Koh was supported by the Mitchell J Notaras Fellowship in Colorectal Surgery awarded by the University of Sydney in cooperation with the Training Board of Colorectal Surgery of the Colorectal Surgical Society of Australia and New Zealand | > 3 anatomical compartments involved, n= 69<br>Conduit= 58<br>Non-PE, n=24<br>Age, years, median= 64<br>Male, n= 16<br>Treatment, n<br>Chemotherapy= 4<br>Radiotherapy= 4<br>Chemotherapy + radiotherapy= 5<br>Palliative surgery (colostomy, ileostomy closure and local excision)= 3<br>No treatment= 6<br><br>**Inclusion criteria**<br>All patients who had recurrent rectal cancer referred for pelvic exenteration (PE) surgery<br><br>**Exclusion criteria**<br>Evidence of distant metastasis or cognitive impairment that prevented them from giving informed consent | | and formation of an ileal or colonic connduit<br>Follow up: "Clinical and baseline QoL assessments were obtained preoperatively and at 1, 3, 6, 9 and 12 months post-operatively."<br>Outcomes: Quality of life<br>Analysis: "To allow for the nonlinearity in the trajectories, piecewise linear models were used, with knots pre-specified at 2 months (after initial recovery from surgery) and at 7 months (when the trajectories tended to flatten out), and an indicator for the pre-discharge assessment. Random effects by patient with unstructured correlations were included for the intercept and the first two time components. For comparison of the mean trajectories between exenteration and non-exenteration patients, a group indicator and a group × time interaction were included in the model."<br>"Patients who had missing 12-month QoL data were excluded from this analysis. Other missing values were completed by multiple imputation using the chained equation method. Twenty imputed datasets were created using 15 iterations. Backward elimination based on Wald tests was used to produce the final adjusted model. Zero was assigned to missing observations due to death and remaining missing observations were excluded." | significance at any one time point)<br>30-day mortality<br>PE= 0/93<br>Non-PE= 0/24<br>12-month mortality<br>PE=15/93<br>Non-PE= 9/24<br>Perioperative complications (including gastrointestinal complications, sepsis or wound complications)<br>PE= 81/93<br>The model using the AQOL utility scores shows that results were similar to SF6D.<br>Baseline AQOL scores, gender and bony resection were significant predictors of AQOL scores 12 months post-surgery | (Missing data for baseline characteristics. For analyses, missing values were completed by multiple imputation using the chained equation method. )<br>Bias in measurement of outcomes: High risk of bias (Outcomes were subjective and recalled on patient recall)<br>Bias in selection of the reported result: High risk of bias (group x time interactions not reported for SF6D scale, data not reported for FACT-C questionnaire)<br><br>**Other information**<br>Indirectness - three (13%) patients in the non-PE group had palliative surgery (colostomy, ileostomy closure and local excision) |

*ASA: American Society of Anaestheologists; (A)QoL: (Assessment of) Quality of Life; IQR: Inter-quartile range; PE: pelvic exenteration; R(0): complete resection; ROBINS-I: Risk of Bias in Non-randomised Studies – of Interventions RT: radiotherapy; SF-6D: Short-Form Six-Dimension: SF-36 – 36 Item Short Form Survey.*

# Appendix E – Forest plots

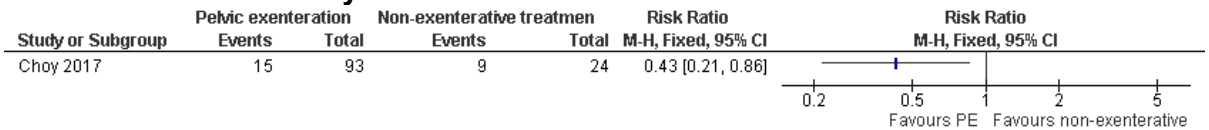
## Forest plots for review question: What is the effectiveness of exenteration for locally advanced or recurrent rectal cancer?

**Figure 2: Comparison: Pelvic exenteration versus non-exenterative treatment – 30-day mortality**



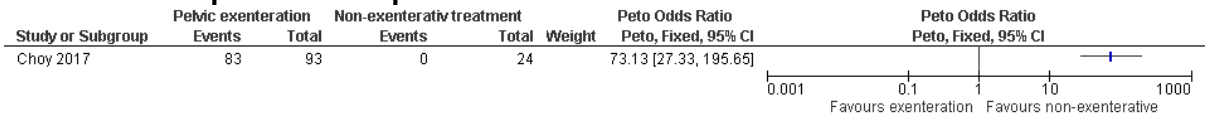

*CI: confidence interval; M-H: Mantel–Haenszel; PE: pelvic exenteration*

**Figure 3: Comparison: Pelvic exenteration versus non-exenterative treatment – 12-month mortality**




*CI: confidence interval; M-H: Mantel–Haenszel; PE: pelvic exenteration*

**Figure 4: Comparison: Pelvic exenteration versus non-exenterative treatment – Perioperative complications**




*CI: confidence interval; PE: pelvic exenteration*

# 1 Appendix F – GRADE profiles

## 2 GRADE profiles for review question: What is the effectiveness of exenteration for locally advanced or recurrent rectal cance

### 3 Table 5: Clinical evidence table for comparison pelvic exenteration versus non-exenterative interventions

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Pelvic exenteration** | **Non-exenterative treatment** | **Relative (95% CI)** | **Absolute** | | |
| **Quality of life - AQoL scale, at 12 months** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | serious[2] | serious[3] | none | Median (IQR) 0.48 (0.07-0.73), n=77 | Median (IQR) 0.14 (0.00-0.54), n=21 | - | not statistically significant | VERY LOW | CRITICAL |
| **Quality of life – SF-6D scale, at 12 months** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | serious[2] | serious[3] | none | Median (IQR) 0.58 (0.33-0.68), n=71 | Median (IQR) 0.53 (0.00-0.62), n=18 | - | not statistically significant | VERY LOW | CRITICAL |
| **Overall survival** | | | | | | | | | | | | |
| 0 | No evidence available | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Local recurrence** | | | | | | | | | | | | |
| 0 | No evidence available | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Distant metastases** | | | | | | | | | | | | |
| 0 | No evidence available | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
| **Disease-free survival** | | | | | | | | | | | | |
| 0 | No evidence available | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
| **Perioperative mortality: 30-day mortality** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | serious[2] | serious[3] | none | 0/93 (0%) | 0/24 (0%) | RD 0.00 (-0.06 to 0.06) | 0 more per 1000 (from 6 fewer to 6 more) | VERY LOW | IMPORTANT |
| **Perioperative mortality: 12-month mortality** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | serious[2] | serious[3] | none | 15/93 (16.1%) | 9/24 (37.5%) | RR 0.43 (0.21 to 0.86) | 214 fewer per 1000 (from 52 | VERY LOW | IMPORTANT |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Pelvic exenteration | Non-exenterative treatment | Relative (95% CI) | Absolute | | |
| | | | | | | | | | | fewer to 296 fewer) | | |
| **Perioperative complications (GI complications, sepsis, wound complications)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | serious[2] | serious[3] | none | 83/93 (87%) | 0/24 (0%) | Peto OR 73.13 (27.33 to 195.65) | 744 more per 1000 (from 540 more to 861 more)[4] | VERY LOW | IMPORTANT |

*AQoL: Assessment of Quality of Life; CI: confidence interval; GI: gastrointestinal; IQR: inter-quartile range; N/A: not applicable; OR: odds ratio; RD: risk difference; RR: relative risk; SF-6D: Short-Form Six-Dimension*

*1 Quality of the evidence was downgraded by 2 because the study did not assess for differences in baseline characteristics; patients self-selected into treatment groups; outcomes were subjective and not all the results were reported*

*2 Quality of evidence was downgraded by 1 because three (13%) patients in the palliative treatment group had palliative surgery (colostomy, ileostomy closure and local excision)*

*3 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (< 300 events for dichotomous outcomes or < 400 participants for continuous outcomes).*

*4 Assumed baseline risk of 5% for perioperative complications of non-exenterative palliative surgery (taken from the evidence review on surgery for asymptomatic primary tumours in metastatic colorectal cancer).*

# Appendix G – Economic evidence study selection

## Economic evidence study selection for review question: What is the effectiveness of exenteration for locally advanced or recurrent 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 review question: What is the effectiveness of exenteration for locally advanced or recurrent 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 effectiveness of exenteration for locally advanced or recurrent rectal cancer?

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

# Appendix J – Economic analysis

## Economic evidence analysis for review question: What is the effectiveness of exenteration for locally advanced or recurrent 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 effectiveness of 3 exenteration for locally advanced or recurrent rectal cancer?

4 **Table 6: Excluded studies and reasons for their exclusion**

| Study | Reason for exclusion |
|---|---|
| Al-Sukhni, E., Attwood, K., Gabriel, E., Nurkin, S. J., Predictors of circumferential resection margin involvement in surgically resected rectal cancer: A retrospective review of 23,464 patients in the US National Cancer Database, International Journal of Surgery, 28, 112-117, 2016 | Not comparative |
| Araujo, Se, Silva, eSousa Ah, Campos, Fg, Habr-Gama, A, Dumarco, Rb, Caravatto, Pp, Nahas, Sc, Silva, J, Kiss, Dr, Gama-Rodrigues, Jj, Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial, Revista do hospital das clinicas, 58, 133-140, 2003 | Comparison not relevant - surgery |
| Austin, K. K. S., Young, J. M., Solomon, M. J., Quality of life of survivors after pelvic exenteration for rectal cancer, Diseases of the Colon and Rectum, 53, 1121-1126, 2010 | Comparison not relevant - either did not have cancer or had colorectal cancer |
| Bakx, R., van Tinteren, H., van Lanschot, J. J. B., Zoetmulder, F. A. N., Surgical treatment of locally recurrent rectal cancer, European Journal of Surgical Oncology, 30, 857-863, 2004 | Not comparative |
| Beaton, J., Carey, S., Solomon, M. J., Tan, K. K., Young, J., Preoperative body mass index, 30-day postoperative morbidity, length of stay and quality of life in patients undergoing pelvic exenteration surgery for recurrent and locally-advanced rectal cancer, Annals of Coloproctology, 30, 83-87, 2014 | Not comparative |
| Bhangu, A., Ali, M., Brown, G., Tekkis, P., Comparison of long-term survival outcomes of operative versus non-operative management of recurrent rectal cancer, European Journal of Surgical Oncology, 38 (11), 1119-1120, 2012 | Conference Abstract |
| Bhangu, A., Ali, M., Cunningham, D., Brown, G., Tekkis, P. P., Comparison of long-term survival outcomes of operative versus nonoperative management of recurrent rectal cancer, Journal of Clinical Oncology. Conference, 30, 2012 | Conference Abstract |
| Bhangu, A., Ali, S. M., Cunningham, D., Brown, G., Tekkis, P., Comparison of long-term survival outcome of operative vs nonoperative management of recurrent rectal cancer, Colorectal Disease, 15, 156-163, 2013 | Population not relevant - 20/70 patients who had surgery |
| Bhangu, A., Ali, S. M., Darzi, A., Brown, G., Tekkis, P. P., Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer, Colorectal Disease, 14, 1457-1466, 2012 | Studies not comparative |
| Bremers, A., Rozema, T., Barentsz, J., Van Krieken, H., Bleichrodt, R., Evaluation of the first results of optimal staging, preoperative (chemo-) radiation and asymmetrical elleptic resection for low rectal cancer evaluated, Colorectal Disease, 2), 43, 2009 | Conference Abstract |
| Christoforidis, D., Horst, P., Pollack, J., Mellgren, A., Rothenberger, D., Madoff, R., Treatment outcomes for recurrent rectal cancer following local or radical primary therapy: A comparative study, Diseases of the Colon and Rectum, 53 (4), 667, 2010 | Conference Abstract |
| Col, C., Hasdemir, O., Yalcin, E., Yandakci, K., Tunc, G., Kucukpinar, T., Sexual dysfunction after curative radical resection of rectal cancer in | Population not relevant - only 1 patient had a pelvic exenteration |

| Study | Reason for exclusion |
|---|---|
| men: The role of extended systematic lymph-node dissection, Medical Science Monitor, 12, CR70-CR74, 2006 | |
| Di Betta, E., D'Hoore, A., Filez, L., Penninckx, F., Sphincter saving rectum resection is the standard procedure for low rectal cancer, International Journal of Colorectal Disease, 18, 463-469, 2003 | Systematic review of studies published pre-2000 |
| Dong, X. S., Xu, H. T., Yu, Z. W., Liu, M., Cui, B. B., Zhao, P., Wang, X. S., Effect of extended radical resection for rectal cancer, World Journal of Gastroenterology, 9, 970-973, 2003 | Intervention not relevant - extended radical resection |
| Dreyer, G., Between cure and palliation: Pelvic exenteration as a treatment modality with limited morbidity, International Journal of Gynecological Cancer, 3), S843, 2011 | Conference Abstract |
| Duraes, L. C., Stocchi, L., Gorgun, E., Costedio, M., Kalady, M., Dietz, D., Church, J. M., Remzi, F. H., Local excision following pelvic imaging vs. radical resection for stage I rectal cancer: Balancing morbidity, survival and recurrence-a matched study, Gastroenterology, 1), S1244, 2016 | Conference Abstract |
| Elagili, F., Dietz, D., Lavery, I., Kiran, R., Pelvic exenteration for primary locally advanced and recurrent rectal cancer: Is it a balance between survival and quality of life?, Diseases of the Colon and Rectum, 56 (4), e274-e275, 2013 | Conference Abstract |
| Eriksen, M. T., Wibe, A., Hestvik, U. E., Haffner, J., Wiig, J. N., Surgical treatment of primary locally advanced rectal cancer in Norway, European Journal of Surgical Oncology, 32, 174-180, 2006 | Population not relevant - patients did not undergo pelvic exenteration |
| Esnaola, N. F., Cantor, S. B., Johnson, M. L., Mirza, A. N., Miller, A. R., Curley, S. A., Crane, C. H., Cleeland, C. S., Janjan, N. A., Skibber, J. M., Pain and quality of life after treatment in patients with locally recurrent rectal cancer, Journal of Clinical Oncology, 20, 4361-4367, 2002 | Outcomes not relevant |
| Gavaruzzi, T., Giandomenico, F., Del Bianco, P., Lotto, L., Perin, A., Pucciarelli, S., Quality of life after surgery for rectal cancer, Early Gastrointestinal Cancers II: Rectal Cancer, Recent Results in Cancer Research. 203, 117-149, 2014 | Book chapter |
| Ghosh, J., Crabtree, S., Murphy, D. J., El-Ghobashy, A., Impact of close resection margins on outcomes of patients who underwent exenteration for recurrent pelvic malignancies; a retrospective analysis and literature review, International Journal of Gynecological Cancer, 1), 507, 2013 | Conference Abstract |
| Gonzalez-Castillo, A., Biondo, S., Garcia-Granero, A., Cambray, M., Martinez-Villacampa, M., Kreisler, E., Results of surgery for pelvic recurrence of rectal cancer. Experience in a referral center, Cirugia espanola, 94, 518-524, 2016 | Not comparative |
| Guimaraes, G. C., Oliveira, R. A. R., Kumagai, L. Y., Baiocchi, G., Aguiar, S., Santana, T. B. M., Zequi, S. C., Favaretto, R. L., Costa, W. H., Lopes, A., Late functional results of Double-barreled wet colostomy after 169 procedures: Single-institution experience, European Urology, Supplements, 12 (1), e557, 2013 | Conference Abstract |
| Harji, D. P., Griffiths, B., Velikova, G., Sagar, P. M., Brown, J., Systematic review of health-related quality of life in patients undergoing pelvic exenteration, European Journal of Surgical Oncology, 42, 1132-1145, 2016 | Systematic review, individual studies checked for inclusion. |
| Harji, D., Griffiths, B., Peter, S., Radical versus ultra-radical surgical strategy in the management of locally recurrent rectal cancer, Diseases of the Colon and Rectum, 58 (5), e189, 2015 | Conference Abstract |
| Harris, C. A., Solomon, M. J., Heriot, A. G., Sagar, P. M., Tekkis, P. P., Dixon, L., Pascoe, R., Dobbs, B. R., Frampton, C. M., Harji, D. P., | Not comparative |

| Study | Reason for exclusion |
|---|---|
| Kontovounisios, C., Austin, K. K., Koh, C. E., Lee, P. J., Lynch, A. C., Warrier, S. K., Frizelle, F. A., The Outcomes and Patterns of Treatment Failure After Surgery for Locally Recurrent Rectal Cancer, Annals of Surgery, 264, 323-9, 2016 | |
| Harris, C., Heriot, A., Sagar, P., Solomon, M., Tekkis, P., Dixon, L., Pascoe, R., Frizelle, F., Patterns of treatment failure after surgery for recurrent rectal cancer, Colorectal Disease, 2), 16-17, 2014 | Conference Abstract |
| Hazard, L. J., Sklow, B., Pappas, L., Boucher, K. M., Shrieve, D. C., Local excision vs. radical resection in T1-2 rectal carcinoma: Results of a study from the surveillance, epidemiology, and end results (SEER) registry data, Gastrointestinal Cancer Research, 3, 105-114, 2009 | Intervention not relevant - no pelvic exenteration |
| Hsu, L. N., Lin, S. E., Luo, H. L., Chang, J. C., Chiang, P. H., Double-barreled colon conduit and colostomy for simultaneous urinary and fecal diversions: long-term follow-up, Annals of Surgical Oncology, 21 Suppl 4, S522-7, 2014 | Population not relevant - only 33% had rectal cancer |
| Kakuda, J. T., Lamont, J. P., Chu, D. Z. J., Paz, I. B., The role of pelvic exenteration in the management of recurrent rectal cancer, American Journal of Surgery, 186, 660-664, 2003 | Not comparative |
| Kang, W. S., Huh, J. W., Min, B. W., Kim, H. R., Kim, Y. J., Comparison of the Oncologic Outcomes of Transanal Excision and Conventional Radical Surgery in Patients with Pathologic Stage I Rectal Cancer, Hepato-Gastroenterology, 61, 660-666, 2014 | Comparison not relevant - both groups received surgery |
| Kessler, H., Matzel, K., Merkel, S., Fietkau, R., Hohenberger, W., 'Watch and wait' as viable option in complete remission of rectal carcinoma after chemoradiotherapy, Colorectal Disease, 5), 9-10, 2011 | Conference abstract |
| Kessler, H., Matzel, K., Merkel, S., Fietkau, R., Hohenberger, W., Results of a "watch and wait" strategy in complete remission of rectal carcinoma after chemoradiotherapy, Diseases of the Colon and Rectum, 56 (4), e205, 2013 | Conference abstract |
| Kessler, H., Merkel, S., Hohenberger, W., Complete remission after neoadjuvant radiochemotherapy in rectal cancer. Radical surgery or "wait and see"?, Diseases of the Colon and Rectum, 52 (4), 774, 2009 | Conference abstract |
| 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 | Comparisons not relevant - both groups had surgery; no pelvic exenteration |
| Kido, A., Koyama, F., Akahane, M., Koizumi, M., Honoki, K., Nakajima, Y., Tanaka, Y., Extent and contraindications for sacral amputation in patients with recurrent rectal cancer: A systematic literature review, Journal of Orthopaedic Science, 16, 286-290, 2011 | Studies not comparative |
| Kusters, M., Austin, K. K., Solomon, M. J., Lee, P. J., Nieuwenhuijzen, G. A., Rutten, H. J., Survival after pelvic exenteration for T4 rectal cancer, The British journal of surgery, 102, 125-131, 2015 | Not comparative |
| Lodin, M., Giannone, G., Treatment of the locally advanced rectal cancer: Abdominal sacral resection, Techniques in Coloproctology, 8, 138, 2004 | Images |
| Madoff, R. D., Extended resections for advanced rectal cancer, British Journal of Surgery, 93, 1311-2, 2006 | Editorial |
| 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 | Comparison not relevant - both groups received surgery |

| Study | Reason for exclusion |
|---|---|
| Pellino, G., Biondo, S., Cazador, A. C., Enriquez-Navascues, J. M., Espin-Basany, E., Roig-Vila, J. V., Garcia-Granero, E., Pelvic exenterations for primary rectal cancer: Analysis from a 10-year national prospective database, World Journal of Gastroenterology, 24, 5144-5153, 2018 | Not comparative |
| Pellino, G., Sciaudone, G., Candilio, G., Selvaggi, F., Effect of surgery on health-related quality of life of patients with locally recurrent rectal cancer, Diseases of the Colon and Rectum, 58, 753-761, 2015 | Comparison not relevant - both arms received surgery |
| PelvEx, Collaborative, Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer: Results from an International Collaboration, Annals of Surgery, 09, 21, 2017 | Not comparative |
| PelvEx, Collaborative, Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer, British Journal of Surgery, 105, 650-657, 2018 | Not comparative |
| Platt, E., Dovell, G., Smolarek, S., Outcome reporting following total pelvic exenteration for the treatment of primary and recurrent locally advanced rectal cancer, Colorectal Disease, 19 (Supplement 2), 111, 2017 | Conference abstract |
| Radwan, R. W., Codd, R. J., Wright, M., Fitzsimmons, D., Evans, M. D., Davies, M., Harris, D. A., Beynon, J., Quality-of-life outcomes following pelvic exenteration for primary rectal cancer, The British journal of surgery, 102, 1574-1580, 2015 | Comparison not relevant - APR vs PE |
| Radwan, R., Jones, H., Codd, R., Evans, M., Davies, M., Harris, D., Beynon, J., Quality of life outcomes following pelvic exenteration and abdominoperineal resection: A prospective comparison study, Gut, 1), A551-A552, 2015 | Conference abstract |
| Rangarajan, K., Bhome, R., Bateman, N., Naga, A., Simon, M., Donovan, K., Smith, J., Mirnezami, A. H., Pelvic exenteration with en bloc resection of the pelvic sidewall and intraoperative electron beam radiotherapy with Mobetron<sup></sup> for locally advanced rectal cancer, Techniques in Coloproctology, 21, 493-495, 2017 | Descriptive study |
| Rausa, E., Kelly, M. E., Bonavina, L., O'Connell, P. R., Winter, D. C., A systematic review examining quality of life following pelvic exenteration for locally advanced and recurrent rectal cancer, Colorectal Disease, 19, 430-436, 2017 | Studies assessed individually |
| Reshef, A., Lavery, I., Kiran, R., Worse oncologic outcomes after abdominoperineal resection when compared to restorative resection for rectal cancer: Tumor biology or technical factors only?, Diseases of the Colon and Rectum, 54 (5), e122-e123, 2011 | Conference abstract |
| Rombouts, A. J. M., Koh, C. E., Young, J. M., Masya, L., Roberts, R., De-Loyde, K., De Wilt, J. H. W., Solomon, M. J., Does radiotherapy of the primary rectal cancer affect prognosis after pelvic exenteration for recurrent rectal cancer?, Diseases of the Colon and Rectum, 58, 65-73, 2015 | Comparisons not relevant - both groups received PE |
| Rutten, H., Is there a need for pelvic exenteration?, European Journal of Surgical Oncology, 36 (9), 795-796, 2010 | Conference abstract |
| Saito, N., Koda, K., Takiguchi, N., Oda, K., Ono, M., Sugito, M., Kawashima, K., Ito, M., Curative surgery for local pelvic recurrence of rectal cancer, Digestive Surgery, 20, 192-199, 2003 | Comparison not relevant - both arms received surgery |
| 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 | Comparison not relevant - TEMS vs RR |

| Study | Reason for exclusion |
|---|---|
| Sajid, S., Leung, P., Craciunas, L., Miles, T., Baig, M. K., Systematic review of studies comparing the effectiveness of trans-anal microsurgery against redical resection in the management of early rectal cancer, Surgical Endoscopy and Other Interventional Techniques, 28, S21, 2014 | Conference abstract |
| Sasikumar, A., Bhan, C., Jenkins, J. T., Antoniou, A., Murphy, J., Systematic Review of Pelvic Exenteration With En Bloc Sacrectomy for Recurrent Rectal Adenocarcinoma: R0 Resection Predicts Disease-free Survival, Diseases of the Colon and Rectum, 60, 346-352, 2017 | Studies assessed individually |
| Simillis, C., Baird, D. L. H., Kontovounisios, C., Pawa, N., Brown, G., Rasheed, S., Tekkis, P. P., A systematic review to assess resection margin status after abdominoperineal excision and pelvic exenteration for rectal cancer, Annals of Surgery, 265, 291-299, 2017 | Studies not comparative |
| Smith, F. M., Al-Amin, A., Wright, A., Berry, J., Nicoll, J. J., Sun Myint, A., Contact radiotherapy boost in association with 'watch and wait' for rectal cancer: initial experience and outcomes from a shared programme between a district general hospital network and a regional oncology centre, Colorectal Disease, 18, 861-870, 2016 | Not comparative; patients did not receive PE |
| Smith, R., Fry, R., Mahmoud, N., Paulson, E., Surveillance after neoadjuvant therapy in advanced rectal cancer can have comparable outcomes with TME, Diseases of the Colon and Rectum, 57 (5), e108-e109, 2014 | Conference abstract |
| Suda, R., Yano, H., Gohda, Y., Miyake, O., Saito, Y., Total pelvic exenteration for primary or recurrent rectal cancer, Colorectal Disease, 4), 5, 2011 | Conference abstract |
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| Uematsu, D., Akiyama, G., Sugihara, T., Magishi, A., Yamaguchi, T., Sano, T., Transanal Total Pelvic Exenteration: Pushing the Limits of Transanal Total Mesorectal Excision With Transanal Pelvic Exenteration, Diseases of the Colon & Rectum, 60, 647-648, 2017 | Editorial |
| Veereman, G., Vlayen, J., Robays, J., Fairon, N., Stordeur, S., Rolfo, C., Bielen, D., Bols, A., Demetter, P., D'Hoore, A., Haustermans, K., Hendlisz, A., Lemmers, A., Leonard, D., Penninckx, F., Van Cutsem, E., Peeters, M., Systematic review and meta-analysis of local resection or transanal endoscopic microsurgery versus radical resection in stage i rectal cancer: A real standard?, Critical Reviews in Oncology/Hematology, 114, 43-52, 2017 | Comparison not relevant - local resection, TAE or TEMS vs RR |
| Verma, K., Engineer, R., Ostwal, V. S., Kumar, S., Arya, S., DeSouza, A., Saklani, A., Post neoadjuvant chemo-radiation positive anterior circumferential resection margin in carcinoma rectum: Extended resection of rectum versus total pelvic exenteration-Results from a single centre retrospective study, Journal of Clinical Oncology. Conference, 35, 2017 | Conference abstract |
| Verma, K., Engineer, R., Ostwal, V., Kumar, S., Arya, S., Desouza, A. L., Saklani, A. P., Persistent involvement of anterior mesorectal fascia in carcinoma rectum - extended resection of rectum vs total pelvic exenteration: results from a single-centre retrospective study, Colorectal Disease, 20, 1070-1077, 2018 | Comparison not relevant to protocol – both groups had surgery |
| Yang, T. X., Morris, D. L., Chua, T. C., Pelvic exenteration for rectal cancer: A systematic review, Diseases of the Colon and Rectum, 56, 519-531, 2013 | None of the included studies were comparative |

| Study | Reason for exclusion |
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| You, Y. N., Habiba, H., Chang, G. J., Rodriguez-Bigas, M. A., Skibber, J. M., Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer, Annals of Surgical Oncology, 18, 989-996, 2011 | Intervention not relevant - only 66% had PE, no stratifications per treatment type |
| Young, J. M., Badgery-Parker, T., Masya, L. M., King, M., Koh, C., Lynch, A. C., Heriot, A. G., Solomon, M. J., Quality of life and other patient-reported outcomes following exenteration for pelvic malignancy, British Journal of Surgery, 101, 277-287, 2014 | Population not relevant - patients had other pelvic cancers |

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# Appendix L – Research recommendations

## Research recommendations for review question: What is the effectiveness of exenteration for locally advanced or recurrent rectal cancer?

No research recommendations were made for this review question.