A systematic review of the pathological determinants of outcome following resection by pelvic exenteration of locally advanced and locally recurrent rectal cancer

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The authors report no conflicts of interest.

Author contributions: LEG, CS, CR conceived the study; All authors contributed to search strategy. LEG and ETP screened studies and performed data extraction. LEG performed data analysis. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Funding: No funding was received to complete this work.

ABSTRACT

Background:

Despite multimodal therapy 5-15% of patients who undergo resection for advanced rectal cancer (LARC) will develop local recurrence. Management of locally recurrent rectal cancer (LRRC) presents a significant therapeutic challenge and even with modern exenterative surgery, 5-year survival rates are poor at 25-50%. High rates of local and systemic recurrence in this cohort are reflective of the likely biological aggressiveness of these tumour types. This review aims to appraise the current literature identifying pathological factors associated with survival and tumour recurrence in patients undergoing exenterative surgery.

Methods:

A systematic review was carried out searching MEDLINE, EMBASE and COCHRANE Trials database for all studies assessing pathological factors influencing survival following pelvic exenteration for LARC or LRRC from 2010 to July 2021 following PRISMA guidelines. Risk of bias was assessed using QUIPS tool.

Results:

Nine cohort studies met inclusion criteria, reporting outcomes for 2864 patients. Meta-analysis was not possible due to significant heterogeneity of reported outcomes. Resection margin status and nodal disease were the most commonly reported factors. A positive resection margin was demonstrated to be a negative prognostic marker in six studies. Involved lymph nodes and lymphovascular invasion also appear to be negative prognostic markers with tumour stage to be of lesser importance. No studies assessed other adverse tumour features that would not otherwise be included in a standard histopathology report.

Conclusion:

Pathological resection margin status is widely demonstrated to influence disease free and overall survival following pelvic exenteration for rectal cancer. With increasing R0 rates, other adverse tumour features must be explored to help elucidate differences in survival and potentially guide tailored oncological treatment.

KEY WORDS: Rectal cancer, exenteration, tumour characteristics

INTRODUCTION

Pelvic exenteration, first described in 1948, refers to radical multivisceral resection of pelvic organs and provides potential cure for patients with locally advanced (LARC) or locally recurrent rectal cancer (LRRC) not amenable to treatment by standard resection(1). Over the past twenty years improvements in technology and surgical technique have allowed successful treatment of what would have been considered irresectable disease suitable only for palliation. En-bloc multivisceral resection and management of extra-mesorectal lymph nodes has evolved in recent years and these procedures are now commonly performed by multidisciplinary specialist teams working in tertiary high-volume units(2). Bony and lateral extension of tumours onto the sacrum, pelvis and pelvic sidewall are no longer contraindications to curative resection. Extensive resections may now include removal of part of the pubic bone, high sacrum (S1/S2) and pelvic side wall vasculature in the pursuit of an R0 resection with acceptable morbidity and mortality(3). Despite these advances a subset of patients with LARC and LRRC continue to have poor survival outcomes despite adequate surgical resection of their disease.

5-10% of patients with colorectal cancer will present with LARC, defined as primary rectal cancer involving or extending beyond the mesorectal plane (b-TME)(4,5). Standard care for LARC involves a combined modality approach with neoadjuvant radiotherapy-based treatment prior to surgery with the aim of facilitating a complete pathological resection, obtaining durable long-term local control(6,7). With multiple advances in the management of LARC, which have primarily improved local disease control, the most frequent site of disease relapse is now distant systemic metastasis

affecting approximately 20-30% of LARC patients(8). The five-year overall survival of patients with LARC remains approximately 65% as a result(9–11).

The rate of local recurrence following primary rectal cancer surgery has thankfully fallen to 5-15% from historic figures of approximately 40% with combined modality treatment(12). However, management of LRRC presents a significant therapeutic challenge and even with modern exenterative surgery, survival rates are poor with 25-50% of patients alive at 5 years(13–15). This is due to high rates of local and systemic recurrence in this cohort reflective of the likely biological aggressiveness of these tumour types.

Multiple influences impact on tumour recurrence and survival including surgical factors from the primary operation, in particular resection margin status; pathological features of the tumour; and use of neoadjuvant or adjuvant chemoradiotherapy(10). Pathological features of the tumour such as its stage, differentiation and lymphovascular invasion are known to impact on the risk of local recurrence(16) and ultimately survival. These elements form part of the routine histopathological examination of a resected tumour and are included in the standardised pathological dataset for reporting primary rectal cancers in the UK(17). Unlike primary rectal cancer there remains no gold standard pathology reporting data set for LRRC which can lead to variation in the quality of tumour specimen reporting(18).

There are other tumour features that are yet to be fully validated that likely contribute to an increased risk of recurrent disease and explain the different outcomes in patients with the same stage and grade of tumour. These include tumour morphology, genomic

and transcriptomic programmes. The ability to more readily identify those patients with high-risk tumours at the outset may permit novel tailored neoadjuvant strategies to be developed. Following resection, additional prognostic information on risk of local or systemic recurrence may inform enhanced surveillance, enabling earlier detection and treatment of recurrent disease to be instituted.

We sought to undertake a review of the published literature to report on the key prognostic determinants of outcome (recurrence and survival) following pelvic exenteration for LARC and LRRC. We were specifically interested in clarifying the role of existing validated pathological assessments in colorectal cancer within these subsets in addition to evaluating whether novel pathological or molecular assessments have been reported in LARC and LRRC.

METHODS

Search strategy

This systematic review was conducted adhering to the recommendations for prognostic factor systematic reviews included in the Cochrane Prognosis Methods Group(19) and the review protocol was registered on Prospero prior to data extraction and analysis of results (PROSPERO 2020 CRD42020223641). This study is also registered with the ResearchRegistry (reviewregistry1358). This report follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR 2 (Assessing the methodological quality of systematic reviews) guidelines in its reporting and was fully compliant with these criteria (20,21).

A comprehensive literature search of EMBASE, MEDLINE, The Cochrane Library and NICE Evidence Search was conducted in July 2021. MESH and keyword search terms included the following: rectal neoplasms and neoplasm recurrence, pelvic exenteration, resection margin, tumour staging, node status, lymphovascular invasion and any other reported pathological factors. The search strategy was conducted with the assistance of an evidence support manager. The full search strategy is shown in supplementary file 1. The search was limited to studies published between January 2010 and July 2021 to prevent overlap with the included studies in the systematic review by Platt et al(22) and to reflect the modern era of pelvic exenteration surgical technique. Language was restricted to English. Hand screening of reference lists of included studies was performed to identify any other relevant papers. Search records were downloaded to a citation manager program (Covidence, Veritas Health Innovation, Melbourne, Australia) and duplicates removed automatically.

The most recent systematic review of outcomes for patients undergoing pelvic exenteration for LARC and LRRC was published in 2018 with a focus on both short and long term outcomes(22). There have subsequently been a number of studies published in this field including large numbers of patients from collaborative multicentre cohorts. There has been a significant change in operative equipment, planning and practice used in pelvic exenteration surgery over the last decade, with increasingly aggressive resection strategies being employed to obtain R0 resections. To accurately reflect modern clinical practice, we have therefore chosen to review papers published after 2010 only.

Eligibility criteria

Randomised controlled trials, and prospective and retrospective observational studies were considered for inclusion in this review. Studies had to report on at least one pathological outcome influencing survival following pelvic exenteration for either LARC or LRRC to be included with at least one year follow up. Studies that included other pathologies such as advanced gynaecological malignancies or anal cancers were only included if the outcomes for rectal cancer were reported separately. All types of pelvic exenteration were included.

Studies were excluded for the following reasons: (1) outcomes of interest were not clearly reported or there were no extractable data, (2) the study included other resection types such as abdomino-perineal resection where results were not separated from those undergoing an exenterative procedure, (3) the outcomes for other pathologies were not reported separately, (4) case series including ten or less patients, conference abstracts, letters, commentaries, and review articles.

The list of collaborators for the large multicentre studies that were included were cross referenced against individual papers. Studies were excluded if their inclusion dates for participants were the same and no additional pathological prognostic findings were reported to prevent cross over of included studies.

Study selection

The titles and abstracts of all studies identified by the search strategy were independently screened by two reviewers [LEG, ETP] and discrepancies resolved by discussion. Full paper screening was performed independently by two reviewers [LEG,

ETP] and papers assessed for eligibility based on the predefined inclusion criteria. Disagreements were discussed with an expert in pelvic exenteration [JTJ] and resolved by mutual agreement.

Data extraction and assessment of bias

Data were extracted onto a predesigned database spreadsheet by two independent reviewers [LEG, ETP]. The following data fields were extracted: first author, year of publication, journal, country of origin, study type, dates of included cases, number of patients and basic demographics including age and sex, length of follow up, cancer type, procedure type, margin status, report factors associated with recurrence, reported factors associated with survival at any reported time point. Each study was assessed for bias using the Quality in Prognostic factors Study (QUIPS) tool where the risk of bias is rated low, moderate, or high for each study against six domains: Study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis(23).

Statistical analysis

Due to the heterogeneity of the studies included meta-analysis was not possible. Therefore, a descriptive review of outcomes has been carried out. The use of multiple different endpoints and definitions for survival and recurrence did not allow for direct comparison of the data across studies.

RESULTS

The initial search strategy identified 169 studies after duplicates were removed. 142 studies were excluded after title and abstract screening leaving 27 papers for full text

review. Eighteen studies were excluded for the following reasons: Two did not separately report pelvic exenteration outcomes from other procedures(24,25), two included non-rectal cancer malignancies without separate analysis of outcomes based on pathology(26,27), ten studies did not have any extractable data relating to the outcomes of interest(28–37), four studies had cross over with the larger multi-centre studies(38–41). Nine met the full inclusion criteria and were included in this review as shown in the PRISMA Diagram (Figure 1).

The nine studies included a total of 2864 patients and were published between 2011 and 2021 (Table 1) (42–50). There were no randomised controlled trials. Of the cohort studies included, one presented prospectively collected data and the remaining eight studies were retrospective. Each study reported on cases spanning a wide number of years ranging from 4 to 27 years. All the included studies were considered to be at risk of moderate bias in at least one domain using the QUIPS assessment tool (Table 2) (23). The cohort sizes ranged from 17 to 1291 patients. There were two large multicentre international cohort studies included that account for the large overall patient number with one reporting outcomes for LARC and the other for LRRC (49,50).

63% of patients were males (n=1793) with a median age of 61 years (range 53-64 years). There were 1622 cases of LARC and 1242 patients with LRRC. The predominant procedure type was: total pelvic exenteration (TPE) 1196 cases; posterior pelvic exenterations (PPE) 999 cases; anterior pelvic exenterations (APE) 110 cases; ‘modified ’pelvic exenterations (not defined by the PelvEx collaborative papers) 230 cases(49,50); supra-levator exenterations 5 cases. In 324 cases the type of exenterative procedure was not stated. Extended bony resection was completed in

359 patients. All nine studies reported the use of neoadjuvant oncological therapies and four (44%) reported adjuvant treatment(39,42–45,51–54). Overall median follow-up was thirty-one months, five papers (56%) did not clearly state length of follow up.

When assessing the relationships between pathological factors and disease outcome we found several studies in which resection margin status (n=7), tumour stage (n=3), lymph node involvement (n=7) and lymphovascular invasion (n=3) were reported in patients undergoing exenteration for LARC or LRRC (Table 3). No other adverse tumour features, other than those in standard reporting datasets for rectal cancer resections, were assessed in relation to their impact on survival or recurrence. No papers were identified that looked at tumour morphology, tumour epigenetics, tumour immunohistochemistry phenotypes or the tumour microenvironment. Additionally, molecular tumour characteristics and their influence on outcome in patients undergoing exenteration for LARC or LRRC have not been considered to date.

Resection margin status

Eight studies (89%) reported on resection margin status(42–46,48–50), however, only seven commented (85%) on the impact of resection margin status on survival(42–44,46,48–50). Across all studies clear resection margins (R0), defined as a clear margin of >1mm, were reported in 1957 of 2674 patients (73%, range 59-91%). The remaining 27% had a positive margin. Distinction between R1 (tumour <1mm from margin edge) and R2 resections (macroscopically involved margin) was not made clear in all studies. Seven studies reported margins separately for primary and recurrent rectal cancer(43–46,48–50). In patients with LARC the overall R0 rate was

83.8% (1254/1495 patients, range of 75-91%)(24–26,29). For LRRC the overall R0 rate was 59.6% (689/1156 patients, range of 59-76%) across four studies(43,45,48,50). No studies commented on whether the location of the positive margin influenced outcome.

Five studies reported that a positive resection margin was a negative prognostic marker for overall survival (OS) (42,43,46,49,50). Three studies compared negative and positive resection margins, where a positive margin may include both R1 and R2 resections(42,43,48). Only one study commented on the impact of resection margin on overall survival in patients with LARC. The PelvEx collaborative reported a HR of 3.01 (95% CI 1.97-4.87, p<0.001) when comparing R0 margins with R2 in this patient group(49).

Four studies commented on resection margin status and OS in patients with LRRC. Like primary tumours a large hazard ratio was seen when comparing an R0 margins with R2 margins (HR 4.84 95% CI 2.77-8.46, p<0.001) in the multi centre PelvEx collaborative paper (50). Ghouti et al also reported a reduction in 1 year OS in patients with LRRC (50% vs 100% p=0.016)(43), whilst Culcu et al found no significant difference at 2 years(48). Hsu reported a significant reduction in OS at 1 year with a positive resection margin combining data for both LARC and LRRC (7.7% vs 97.3%, p=0.001) (42).

Two studies assessed the impact of the resection margin on disease free survival (DFS), both demonstrating a reduction in survival (43,46). When R0 resections were compared with positive margins, Kazi et al reported a hazard ratio for 3-year DFS of

3.001 (1.593-5.651, p=0.0007) on univariate analysis, although this lost significance upon multivariate modelling in patients with LARC (46). Ghouti et al reported 1-year DFS of 82% following R0 resection, compared with only 10% for patients with LRRC with a positive resection margin (p<0.001)(43). In-keeping with these observations, Pellino et al. found that a positive margin greatly increased the risk of 5-year local recurrence (HR 5.58, 95% CI 1.04-30.07, p=0.04) for patients with LARC(44).

Tumour stage

Four papers (44%) commented on the impact of tumour stage on survival(43,45–47). In patients with LARC, Koda et al found no significant difference in 5-year survival between those with T3 or T4 disease (67.2% vs 51.2%, p=0.24) (47). Domes et al also found no significant influence of tumour stage on survival in their mixed cohort of patients with LARC and LRRC(45).

The effect of tumour stage on outcomes in LRRC is also unclear. Only one small study (n=17) found advancing tumour stage to significantly reduce survival (when applying the 8th TNM classification despite looking at recurrent tumours)(48). However, Ghouti et al found no association of tumour stage on either 1 year DFS (60% vs 50%, p=0.77) or OS (87% vs 75%, p=0.59) when comparing UICC stage 2 and stage 3 disease (43).

Nodal disease

The influence of nodal disease on outcomes was reported in seven studies (78%), four of which were in patients with LARC(44,46,47,49), and three in patients with LRRC(43,48,50).

In patients with LARC, all four studies found that positive lymph nodes were a negative prognostic marker although this only reached significance in three studies.(44,46,47,49). Overall, 38% of patients has node positive disease (n= 434/1150). Koda et al found that 5-year OS and DFS were reduced when comparing N0 with N1 and N2 disease on multivariate analysis with relative risks of 0.370 (95%CI 0.147-0.934, p=0.035) and 0.275 (95%CI 0.117-0.646, p<0.01), respectively(47). Kazi et al reported a HR of 2.324 (95%CI 1.419-3.805, p= 0.0008) for 3 year DFS but the significance was lost on multivariate analysis(46). PelvEx reported OS was reduced from 58% to 44.3% at 3 years and from 39.7% to 28.9% at five years when comparing node negative and node positive disease with a HR of 1.27 (95%CI 1.06-1.52, p=0.009) on multivariant analysis(42).

Three studies reported the effect of nodal disease in patients with LRRC with 26% of patients overall having positive nodes (n=99/381)(43,48,50). Interestingly the presence of nodal disease appears to have less impact in LRRC than LARC with two of the studies not reporting a significant effect of nodal disease on OS with follow up of 1-2 years(43,48,50). Although the PelvEx study has longer follow up and demonstrated significance of node positive disease on 3- and 5-year OS (21% vs 38%, 11% vs 22.8%, p=0.014, respectively) in univariate analysis this was lost on their multivariate model(50).

Lymphovascular invasion

Three studies discussed the effect of lymphovascular invasion (LVI) on outcome which was present in 24.6% of patients (n=50/203)(45,46,48). All found a significant association between its presence and survival.

Kazi et al reported on patients with LARC a 3 year DFS HR of 2.843 (95%CI 1.64-4.928, p= 0.0002) but this effect was lost on multivariate analysis (HR 1.663, 95%CI 0.847-3.264, p=0.143)(46). Culcu demonstrated a statistically significant reduction in overall survival at 2 years with LVI in patients with LRRC (80% vs 16.7%, p=0.038)(48). Domes et al demonstrated a significant association between LVI and OS (p=0.012) and DFS (p<0.001) on univariate analysis but only DFS on multivariate analysis with a HR 7.9 (95%CI 2.4-26.7, p<0.001) for a cohort including both LARC and LRRC(45).

Other factors

The effect of tumour differentiation on outcomes was explored by two studies. Poorly differentiated or signet ring tumours were found to be a negative prognostic marker with reduced 3-year OS in patients with LARC: HR 2.10 (95%CI 1.061-4.643, p=0.031) on multivariate analysis(46). However, no significant effect was noted for 1 year OS (83% vs 80%, p=0.902) in patients with LRRC when comparing well differentiated to moderately differentiated lesions (43).

Perineural invasion and its impact on overall survival was reported in two studies affecting 21% (n=37/175) of patients. Kazi et al found no significant impact of perineural invasion on 3-year DFS in patients with LARC (HR 1.693, 95%CI 0.952-3.01, p=0.073)(46). However, Culcu et al reported it to be a negative prognostic marker with reduced 2-year OS in patients with LRRC, 83.3% vs 15.2%, p=0.022(48).

The final pathological factor to be reported on was tumour regression (TRG) following neoadjuvant therapy in patients with LARC by Kazi et al using Mandard's classification(55). A TRG score greater than 3, present in 40.8% (n=60) patients with LARC in their cohort, was a negative prognostic marker. TRG >3 was associated a reduction in 3-year DFS with a HR 2.214 (95%CI 1.124-4.36, p=0.02) on multivariate analysis(46).

DISCUSSION

Pelvic exenteration has improved the survival of patients with LARC and LRRC. However, this review demonstrates that, despite improvements in operative technique, there is still relatively little known about adverse pathological tumour features that impact on long term survival and recurrence for patients with LARC and LRRC. Other than details included in standard pathology reporting there are no other published reports of pathological factors contributing to reduced survival or recurrence in patients undergoing PE for LARC or LRRC.

This review highlights several pathological factors that are considered to influence outcome, including resection margin status, lymph node involvement and lymphovascular invasion. Most studies demonstrate a significant association between an incomplete excision and reduced survival. It is, however, difficult to assess if there has been an improvement in R0 rates over time due to the large range of dates over which patients included in studies had their surgery. This ranged from four to twenty-seven years in this review. It may be anticipated that R0 resection margin status would have improved over the last two decades with improved preoperative scanning, increasingly rigorous multidisciplinary decision making in relation to operative

planning, and advances in operative equipment and technique. However, this is difficult to prove from the available literature. A recent multicentre study found no significant increase in R0 resection rates over time, but this is in the context of increasingly radical resections and therefore may not be an accurate reflection due to confounding(56). The presence of nodal disease appears to be a negative prognostic marker, especially in the LARC subset in addition to lymphovascular invasion. Tumour stage appears less important and failed to influence outcomes across the published literature.

The studies published over the last ten years demonstrate an often non standardised approach to reporting and data is largely collected retrospectively which in turn limits the ability of researchers to extrapolate sound conclusions and is associated with inherent bias. More recently this has been addressed with large multicentre cohort studies such as those coordinated by the PelvEx collaborative(49,50). The significant contribution of these multinational studies provides greater weight of evidence when scrutinising the data available in the literature. We appreciate that the majority of patients presented in this review come from these two large multicentre studies. However, we felt the present review was necessary because features likely to be important for outcome such as tissue regression score, perineural invasion and lymphovascular invasion were presented in the additional studies.

As our understanding of tumour biology and host response to disease increases, we must now assess for novel prognostic metrics. These cancer subtypes are inherently aggressive demonstrating a propensity for local invasion or recurrence. Tumour

genotyping and epigenetic characteristics are promising potential markers that could influence future survival. Despite increasing evidence of the impact of the host systemic inflammatory response and primary colorectal cancer outcomes(57), little is published in relation to its effect in patients with LARC or LRRC. Novel metrics which have shown promise in primary colorectal cancer include preoperative systemic inflammatory markers such as neutrophil to lymphocyte ratio or the modified Glasgow Prognostic Score and local tumour inflammatory status such as stromal deposition(57,58). These biomarkers may be of increased importance in advanced disease due to the inflammatory response promoted by tumour perforation and invasion of neighbouring structures. Other tumour biomarkers have been identified for LARC that may help predict those patients who respond to neoadjuvant chemoradiotherapy and influence survival(59). These factors have not been reported in the context of outcomes following exenterative surgery. Further work is also required to gain a greater understanding of the tumour biology of recurrent rectal cancers to identify if adverse features were present in the primary resected tumour.

Advances in primary rectal cancer understanding and prognostication have seemingly yet to be investigated in patients with LARC or LRRC undergoing pelvic exenteration. Ultimately robust prospective case-controlled studies should be designed to evaluate novel metrics which may allow more efficient and accurate prognostication of DFS and influence treatment decision making processes in future. Such metrics will allow a more frank and informed discussion with patients who are often reluctant to undergo what is potentially a high risk, high morbidity procedure that may ultimately be futile. The ability to more accurately counsel patients on the risks of surgery and tumour recurrence based on their individual tumour biology is likely to represent the future of

personalised oncological care. Improved knowledge of tissue biomarkers for local recurrence would enable better treatment allocation and guide the need for enhanced surveillance. This may allow earlier detection and treatment of recurrent disease and in the setting of further recurrence, identify those who may suitably cohabit with their disease for prolonged periods of time.

Study limitations

Despite restricting our publication status to papers published after 2010, to reflect modern pelvic exenteration practice, several historic patients from as far back as 1986 were included. Many changes in patient selection, oncological therapy, use of MRI, surgical technique, and pathology reporting over this time will affect the results from these studies and may reduce the generalisability to pelvic exenterations performed today. However, these patients represent a minority of the overall patient cohort with less than 60 patients (2%) included prior to 2000.

Meta- analysis was unable to be performed due to the different end points and timing of end points reported in the included studies. Multiple different prognostic factors were used in multivariate analysis that were different across all studies. The definition of what constitutes a pelvic exenteration was not included in all studies and given the nature of the disease, and the complexity of surgery, the operations are likely to be different. This lack of classification adds to the heterogeneity of the presented data. Assessment of publication bias was not possible as fewer than 10 studies are included.

CONCLUSION

Radical resection by pelvic exenteration is often the only available potentially curative treatment for patients with LARC and LRRC. These operations incur high morbidity and historically significant mortality therefore should be undertaken where a high likelihood of improved survival and maintained quality of life is achievable. Defining identifiable baseline determinants of outcome and survival are therefore vital in ensuring patients are counselled appropriately. Resection margin status remains the most reliable prognostic marker of overall survival. In the setting of increasing R0 rates, other clinicopathological factors that influence disease will become more relevant to outcome and must be investigated further as part of well-constructed large multinational observational studies to help improve survival and further guide treatment in this patient group. Further investigation should also focus on novel biomarkers and genetic factors which may play an important role in the potential for disease to recur.

Acknowledgments: With thanks to Megan McCarthy, Evidence Support Manager, The Royal College of Surgeons of England Library and Archives Team, for conducting the literature searches

Provenance and peer review: Not commissioned, externally peer-reviewed

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Table 1: Summary table of all included studies

Publication			Study setting			Included patients		Demographics		Cancer type		Procedure type							Reported follow up period	Funding
1st Author	Year	Journal	Study type	Single or multi-centre	Country	Year of included patients	Total number patients	Male	Age (years)	LARC	LRRC	TPE	PPE	APE	MPE	SLE	Other/ unknown	Bone resection		NS
Hsu	2011	Asian Journal of Surgery	RC	Single	Taiwan	1991-2007	23	23	57.6	13	10	18	0	0	0	5	0	1	1yr OS	NS
Domes	2011	Canadian Journal of Surgery	RC	Single	Canada	1997-2007	28	25	61	24	4	28	0	0	0	0	0		3yr OS, DFS	NS
Ghouti	2015	The American Journal of Surgery	RC	Single	France	2004-2010	27	18	58	0	27	14	13	0	0	0	0	12	1yr OS, DFS	NS
Koda	2016	International Journal of Colorectal Disease	RC	Single	Japan	1986-2013	54	48	64	54	0	54	0	0	0	0	0	0	5yr OS, DFS	Japanese Ministry grant
PelvEx Collaborative	2018	British Journal of Surgery	RC	Multi (27 centres)	Worldwide	2004-2014	1184	752	63	0	1184	418	395	80	91	0	200	240	3yr OS, 5yr OS	NS
Pellino	2018	World Journal of Gastroenterology	PC	Multi-national registry	Spain	2006-2017	82	54	61.8	82	0	0	0	0	0	0	82		5yr LR, OS, DFS	NS
PelvEx Collaborative	2019	Annals of Surgery	RC	Multi (27 hospitals)	Worldwide	2004-2014	1291	778	63	1291	0	551	529	30	139	0	42	106	3yr OS, 5yr OS	NS
Culcu	2021	Turkish Journal of Colorectal Disease	RC	Single	Turkey	2015-2019	17	8	53.4	0	17	17	0	0	0	0	0	0	1yr OS, 2yr OS	No funding
Kazi	2021	British Journal of Surgery	RC	Single	India	2013-2020	158	87	44	158	0	96	62	0	0	0	0	0	3yr DFS	NS
						TOTAL	2864	1793	61	1622	1242	1196	999	110	230	5	324			

RC- Retrospective cohort, PC- Prospective cohort, LARC- Locally advanced rectal cancer, LRRC- Locally recurrent rectal cancer, TPE- Total pelvic exenteration, PPE- Posterior pelvic exenteration, APE- Anterior pelvic exenteration, MPE-Modified pelvic exenteration, SLE- Supralevator exenteration, NS- Not stated, OS- Overall survival, DFS-Disease free survival LR- Local recurrence

Table 2: The risk of bias assessment of included studies using QUIPS tool

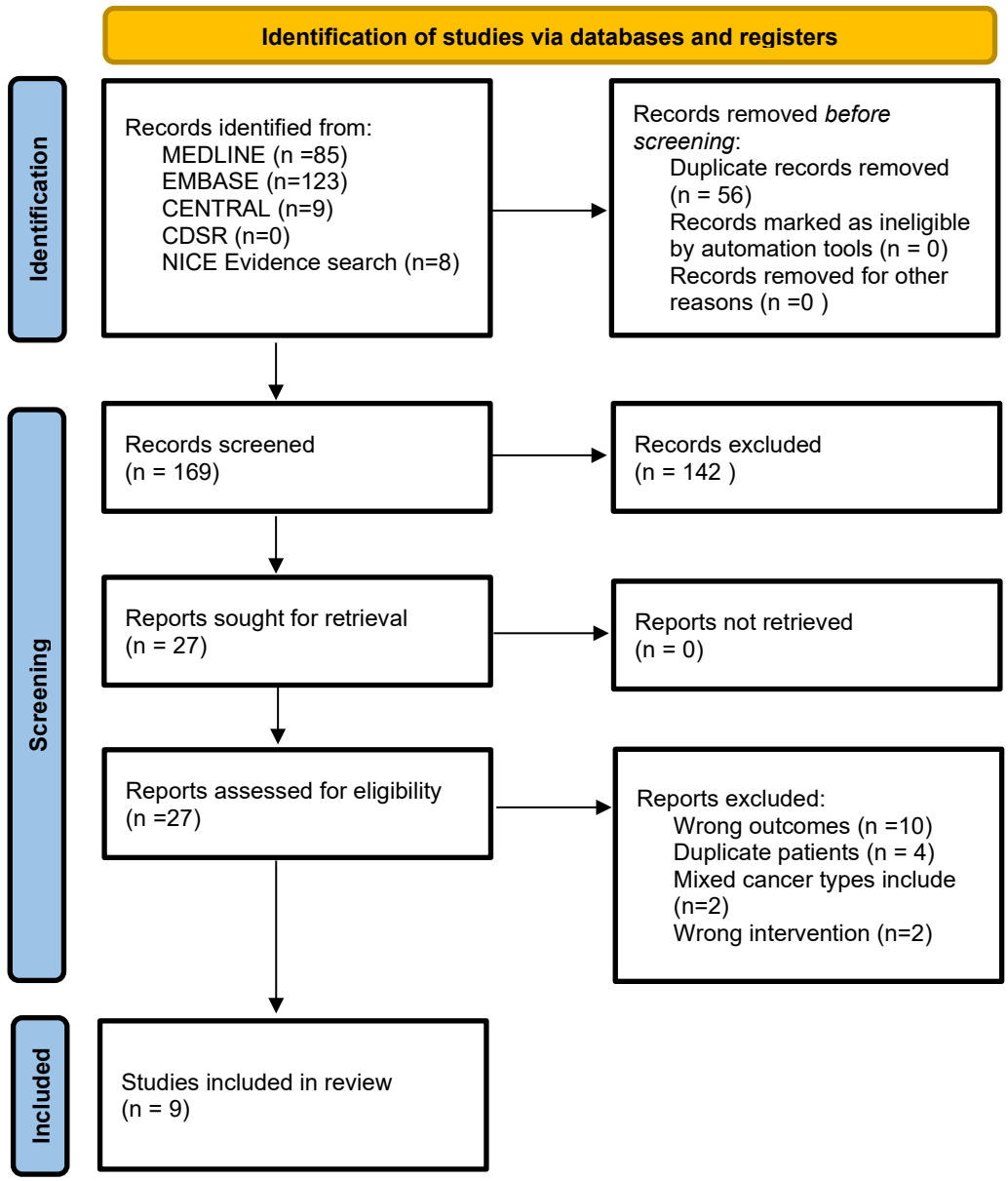
Study	Study population	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Chiang 2011	Low	Low	Low	Low	Moderate	Moderate
Domes 2011	Low	Low	Low	Low	Low	Low
Ghouti 2015	Low	Low	Low	Low	Moderate	Moderate
Koda 2016	Low	Low	Low	Low	Low	Low
PelvEx Collaborative 2018	Low	Moderate	Low	Low	Low	Low
Pellino 2018	Low	Moderate	Low	Low	Moderate	Moderate
PelvEx Collaborative 2019	Low	Moderate	Low	Low	Low	Low
Culcu 2021	Low	Low	Low	Moderate	Moderate	Moderate
Kazi 2021	Low	Low	Low	Low	Low	Low

Table 3. Pathological factors assessed in each study

	Tumour pathological factors assessed					
First author	Resection margin	Nodal disease	Lymphovascular invasion	Tumour stage	Differentiation	Other
Hsu 2011	Y*	N	N	N	N	
Domes 2011	N	N	Y*	Y	N	
Ghouti 2015	Y*	Y	N	Y	Y	
Koda 2016	N	Y*	N	N	N	
PelvEx Collaborative 2018	Y*	Y*	N	N	N	
Pellino 2018	Y*	Y	N	N	N	
PelvEx Collaborative 2019	Y*	Y*	N	N	N	
Culcu 2021	Y	Y	Y*	Y	N	Perineural invasion
Kazi 2021	Y*	Y*	Y*	N	Y*	Tumour regression score, perineural invasion

*= statistically significant effect on survival

Figure 1: PRISMA 2020 flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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