LOCAL VERSUS RADICAL SURGERY FOR EARLY RECTAL CANCER WITH OR WITHOUT NEOADJUVANT OR ADJUVANT THERAPY

by

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Abstract

Background: Total mesorectal excision is the standard of care for Stage-I rectal cancer. Despite major advances and increasing enthusiasm for modern endoscopic local excision (LE), uncertainty remains regarding its oncologic equivalence and safety relative to radical resection (RR).

Methods: We performed a comprehensive search of major electronic databases, trial registries, and grey literature for randomized controlled trials (RCT) comparing LE versus RR with or without use of neo/adjuvant chemoradiotherapy. We used standard Cochrane Collaboration methodological procedures. Oncologic, surgical, and functional outcomes were sought and compared using a generic inverse variance and random-effects models, where appropriate.

Results: Of eight potential studies, only three RCTs were complete and included in data synthesis with a combined total of 211 patients. Risk of bias was judged as unclear for oncologic outcomes across studies and high for surgical morbidity outcomes. Disease-free survival was comparable between LE versus RR (hazard ratio (HR) 1.48, (95% confidence interval (CI) 0.54 to 4.02; low-quality evidence, translating into 8.1% vs. 5.6% disease recurrence after LE and RR, respectively). Similarly, there was no difference between LE versus RR in cancer-related survival, local recurrence-free survival, or metastasis-free survival. There were no cases of 30-day mortality after any of the interventions. Risk of major postoperative complications was not significantly lower with LE (risk ratio 0.56, 95%

CI 0.21 to 1.51; very low-quality evidence; corresponding to 5.2% for LE vs. 9.3% for RR). Very low-quality evidence suggested a non-significant trend for fewer minor postoperative complications after LE (risk ratio 0.53, 95% CI 0.28 to 1.03; very low-quality evidence; corresponding to 16.2% for LE vs. 30.6% for RR). One study reported 24% rate of definitive stoma only after RR. Data suggested shorter length of stay after LE. No objective data was available regarding sphincter function, quality of life or genitourinary function in any of the studies.

Conclusion: Based on limited and low to very low-quality evidence, this review suggests an equal role for LE in terms of oncologic and operative outcomes in patients with early-stage rectal cancer. If further supported by more RCTs, LE has the potential to become the preferred approach in these patients.

Lay Summary

Question: Despite major advances in less-invasive rectal cancer surgery techniques by local excision (LE), complete removal of the diseased rectum by radical resection (RR) has remained the standard of care for early-stage rectal cancer due to uncertainty about LE's safety.

What was done: We conducted a systematic review of literature for high-quality studies that compared LE to RR in patients with early rectal cancer. Results were pooled to compare oncologic outcomes, major and minor postoperative complications, and functional outcomes.

Results: Data from 3 trials showed no differences between the two approaches in terms of disease-free survival after treatment, recurrence rates, metastasis rates, and overall survival. Postoperative complications were comparable with a trend towards fewer minor complications after LE. None of the studies reported quantitative results for functional outcomes.

Conclusion: This meta-analysis suggests LE is equally safe and effective for the treatment of early rectal cancer based on the available evidence.

Preface

The dissertation is the original, independent, unpublished work by the author, Seyed Mohammad Ali Kalantar Motamedi. I developed the idea, drafted the protocol, undertook the review, collected the data, analyzed the data, and drafted the final manuscript. Dr. Nicole Mak served as the second review author for this project who helped in study screening and data collection. Dr. Terry Phang acted as the third and adjudicating reviewer and provided guidance and feedback in all stages of the work as my supervisor. Other surgeons at St. Paul's Hospital's Colorectal Research Group also provided insight and shared their expertise on the topic at weekly research meetings. This manuscript presents the final and approved results of the project based on the latest update of the search in July 2019.

An e-poster based on parts of Chapters 3 and 4 was presented at the American Society of Colo-Rectal Surgeons (ASCRS) 2019 Annual meeting in Cleveland, OH in June 2019 (Motamedi, A K; Mak, NT; Brown, CJ; Raval, MJ; Karimuddin, AA; Phang, T. Systematic Review and Meta-Analysis of Local Versus Radical Surgery for Early Rectal Cancer with or without Neoadjuvant or Adjuvant Therapy). Another e-poster based on Chapter 4 of this work was presented at the Canadian Surgery Forum 2019 in Montreal, QB (M Ali K Motamedi, Nicole T Mak, Carl J Brown, Manoj J Raval, Ahmer A Karimuddin, P Terry Phang. Local versus Radical Surgery for Early Rectal Cancer with or without Neoadjuvant or Adjuvant Therapy: A Systematic Review and Meta-analysis).

This project did not require any institutional ethics approval.

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List of Abbreviations

C-RS	Cancer-related survival
CRT	Chemoradiotherapy
D-FS	Disease-free survival
LE	Local excision
LOS	Length of stay
LR-FS	Local recurrence-free survival
M-FS	Metastasis-free survival
OS	Overall survival
RCT	Randomized controlled trial
RR	Radical resection
SoF	Summary of findings
TAMIS	Transanal minimally invasive surgery
TEM	Transanal endoscopic microsurgery
TEO	Transanal endoscopic operation
TME	Total mesorectal excision
TSPM	Transanal single-port microsurgery

Glossary

Local excision (of rectal cancer)	The surgical/endoscopic approach by which the tumour is removed intraluminally through an anal port by utilization of rectal insufflation and stereoscopic visualization, enabling an accurate transmural removal of the tumour but not the entire mesorectum.
Radical resection (of rectal cancer)	The surgical operation achieving TME either through an abdominal incision (open), abdominal laparoscopic, or double-team abdominal-transanal.
TAMIS (Transanal minimally invasive surgery) and TSPM (Transanal single-port microsurgery)	The rectal tumour is excised and removed through an anal port (single-incision laparoscopic surgery port (SILS port) or GelPOINT Path Transanal Access Platform) to establish pneumorectum and by using ordinary laparoscopic instruments, including graspers, thermal energy devices, and needle drives
TEM (Transanal endoscopic microsurgery)	The rectal tumour is removed through a 4cm rigid rectoscope to establish pneumorectum and by using an oblique-angled stereoscopic endoscope with modified surgical instruments.

TEO (Transanal endoscopic operation)	A modification of TEM that uses a similar platform to TEM but with regular laparoscopic instruments to remove the tumour through the rigid rectoscope.
Total mesorectal excision (TME)	The surgical approach by which the affected part of the rectum harbouring the tumour along with the surrounding mesorectal envelope is removed en-bloc.

Acknowledgements

I would like to offer my gratitude to my supervisor, Dr. P. Terry Phang who masterfully and patiently orchestrated the many steps of this research and guided me along the way. I would also like to thank all the colorectal surgeons at St. Paul's hospital, Drs. Carl Brown, Ahmer Karimuddin, and Manoj Raval who provided much support and feedback whenever needed. The relentless commitment of the many colorectal research coordinators at the department of surgery at St. Paul's hospital to perfecting research projects benefited me extensively.

I would also like to thank the current and previous editors of the Cochrane Colorectal Cancer Group for their support and guidance on this project, as well as Mr. Lovedeep Gondara of Surgical Oncology Network, BC Cancer Agency, British Columbia for helping with some statistical aspects of the review. I also offer my gratitude to Ms. Kathryn Hornby of the Woodward Library, UBC Vancouver who assisted me in undertaking the literature search for this project.

Lastly, special thanks to my parents, my role model physicians living thousands of kilometres away, whose care and support blessed me emotionally and financially, as well as my partner, Ine Beljaars, who kept me company through hard times and generously and unconditionally shared her time and energy with me and helped me in my career path.

Dedication

I dedicate this work to all patients affected by rectal cancer, who would benefit from surgical research and innovation.

Chapter 1: Introduction

1.1 Background

1.1.1 Description of the condition

Colorectal cancer is a public health concern worldwide. It is the third overall most frequent cancer with more than 1.8 million new cases globally and the second leading cause of cancer deaths with 880,792 cases in 2018 [1, 2]. There were more than 13,000 males and 11,500 females affected by colorectal cancer in Canada in 2018 [2]. In contrast to the decrease in overall incidence and mortality rate for colorectal cancer over the past few decades, these rates among patients younger than 55 years are increasing at an annual rate of 2.4% and 1%, respectively [3]. Rectal cancer accounts for 35% of colorectal cancer cases and is also expected to increase in both genders [4].

These concerning figures have fostered major advances in screening programs and diagnostics. As a result, approximately one-third of rectal cancer patients present with early and localized stage-I cancer, i.e. a tumour confined to superficial layers (submucosa (T1) or muscularis prorpia (T2)) of the rectal wall without any evidence of local lymph node spread or distant metastasis [5]. Stage-I cancer thus makes up a significant percentage of rectal cancers and has a 5-year survival rate of about 90% [3, 6].

This favourable survival statistic, however, is derived from populations undergoing standard "radical resection" of rectal cancer, by which the tumour and regional lymph nodes are removed. Since stage-I rectal cancer is generally characterized by the absence of any local

spread, this radical approach may seem an over-treatment for this subset of patients. However, it has recently been reported that even clinical T1-2N0M0 rectal cancers can have undetected lymph node involvement rates of 6% to as high as 65% and 11% to 78%, for T1 and T2 tumours respectively, depending on the presence of high-risk pathologic features in the tumour [7, 8]. Radical resection thus minimizes the risk of any residual disease and hence recurrence by removing all the possibly involved lymph nodes [9].

1.1.2 Description of the intervention

Radical resection of the rectum is performed according to principles of total mesorectal excision (TME), by which the tumour and all lymph nodes around the rectum are precisely removed as a whole within a mesorectal fascial envelope [10]. TME principles are strictly followed in all radical surgery methods including Hartmann's resection, low anterior resection, or abdominoperineal resection, which may be performed through the abdomen using open, laparoscopic, hand-assisted laparoscopic, or robotic techniques. More recently, TME has also been performed by a two-phase transabdominal-transanal approach: transanal TME (TaTME) [11-13].

Radical surgery emerged as the standard of care since it significantly reduces local recurrence and improves the oncologic results for rectal cancer patients [10]. It is, however, associated with considerable morbidity not only from the operation itself but also from the resulting functional impairment. Transabdominal rectal surgery involves incising through the abdominal wall necessitating hospital admission for pain control, intravenous fluids, and recovery. It also requires an anastomosis that is challenging to perform transabdominally

especially for low-lying rectal tumours and carries a risk of leakage and sepsis. Resection of the rectum and consequent loss of rectal reservoir function, furthermore, may result in abnormal bowel habits (low anterior resection syndrome) and fecal incontinence. Lastly, injury to autonomic nerves during pelvic surgery may cause urinary incontinence and sexual dysfunction in a significant number of patients [14, 15]. While utilization of radical surgery is currently justified due to its oncologic superiority in patients with invasive rectal cancer with a high probability of local spread, its use in early rectal cancers that may not require an extensive lymph node removal is increasingly being challenged due to its associated postoperative morbidity.

In contrast to radical surgery, local excision avoids an abdominal incision, risk of an anastomotic leak, and functional problems of a pelvic resection by solely targeting and removing the tumour through the anus. This less-invasive approach is thus associated with fewer postoperative complications compared with radical surgery, 5.6% vs. 14.6%, respectively [16]. However, traditional "open" transanal excision [17] was associated with an unacceptably high local recurrence rate of up to 30%, compared to a low rate of 2-4% with radical surgery [18-21]. Improved visualization could be achieved using transsphincteric and trans-sacral approaches but these were associated with a high rate of fistula formation [22]. Recent technologic advances, however, have offered improved visualization for transanal local excision through insufflating the rectum and magnification of the lesion. The first technical advance was the introduction of transanal endoscopic microsurgery (TEM) manufactured by Wolf and utilized by Professor Buess in Germany [23], which incorporates a rigid proctoscope with optics enabling clear visualization and magnification of the lesion with 3D depth perception. At present, several other platforms also provide equipment for

transanal excision using the same concepts including transanal endoscopic operation (TEO), transanal minimally invasive surgery (TAMIS), and transanal single-port microsurgery (TSPM). TEM and TEO use rigid proctoscopes and TAMIS and TSPM use flexible anal ports with laparoscopic instruments [24-26]. While these transanal procedures, similarly, cannot achieve TME from a technical standpoint, their improved visualization and higher accuracy decrease positive resection margins and hence, local recurrence rates, approaching radical TME surgery results [27-29].

1.1.3 How the intervention might work

Since local excision does not treat potential metastases to regional lymph nodes and a chance of local spread remains, neo/adjuvant chemoradiotherapy (CRT) may be utilized to improve local control and thus survival for local excisions. [30-34]. CRT may be rationally applied for T1 and T2 cancers with higher risk pathological features including poor differentiation, lymphovascular invasion, and tumour budding [35].

1.2 Why it is important to do this review

While a number of studies and reviews, e.g. [36], have sporadically evaluated some of the surgical techniques for early rectal cancer, we aimed to systematically summarize the evidence on safety and efficacy of the radical versus local approach. Considering that local excision is increasingly being adopted worldwide, it should accurately and regularly be evaluated using the high-quality Cochrane methodology to ensure it is at least equally effective oncologically to justify its major advantage of less invasive nature. With the

addition of neo/adjuvant CRT to treatment protocols, it is also important to determine whether CRT enables the use of local excision techniques for tumours with high-risk features or higher-grade tumours (T2). Their equal safety and efficacy would potentially translate into safer surgery, fewer sphincter and genitourinary complications, and better quality of life, all important outcomes from the patients' perspective [37]. Given the rapid advances in technology and surgical techniques, It is necessary and timely that we assess and summarize the short and long-term outcomes from recent trials to support the continued use of this approach as an equivalent or superior option to radical surgery for patients with early rectal cancer.

1.3 Objectives

To assess the safety and effectiveness of local surgical excision compared with radical surgical resection in patients with early rectal cancer.

Chapter 2: Methodology

2.1 Design

This study is a systematic review and meta-analysis of randomized controlled trials (RCTs) that compare LE to RR.

2.1.1 Types of eligible studies

We included RCTs that compare local excision and radical resection for early rectal cancer. Published and unpublished studies, as well as non-English studies, were eligible for inclusion.

Cluster-RCTs, which are an unsuitable and unlikely design, and studies that do not report separate data for benign and malignant lesions were excluded. Studies that included only a subset of relevant participants were considered for inclusion based on the availability of separate data for those participants in the article or upon request from the authors.

2.1.2 Eligible participants

Participants aged 18 years or older who had radical resection or local excision for rectal cancer - defined as a tumour with distal extension to ≤15 cm from the anal verge (measured by sigmoidoscopy) – at an early stage were included, defined as:

- Stage-I (T1-2N0M0, TNM staging system) (American Joint Committee on Cancer 2017), or
- Stage A (Dukes staging system) [38]

We excluded participants with stage 0 (TisN0M0) rectal cancer, as well as participants with locally advanced cancer (stage II and higher), synchronous lesions, recurrent cancer, or tumour types other than adenocarcinoma.

2.1.3 Eligible interventions

Local excision implies full-thickness excision of the lesion with free margins and with curative intent using any of the aforementioned local excision techniques: TEM, TEO, TAMIS, or TSPM.

Radical resection techniques served as standard control interventions. Procedures such as Hartmann's resection, low anterior resection, and abdominoperineal resection, which accomplish complete resection of the rectum with regional lymph nodes within the mesorectal fascia (i.e. TME) using the open, laparoscopic, robotic, or TaTME approach, were considered.

The use of CRT was permitted in one or both arms of the study, i.e. not required to be applied equally, which necessitated three comparisons to be made:

- Local excision vs. radical resection
- CRT + Local excision vs. radical resection

- CRT + Local excision vs. CRT + radical resection

2.1.4 Outcomes measures

2.1.4.1 Primary outcomes

1. Disease-free survival (D-FS) [defined as the chance that a patient is without local recurrence or metastasis at a given time point]
2. Sphincter function: as measured by standardized scales such as the Wexner scale [39] and low anterior resection syndrome score (LARS score) [40]

2.1.4.2 Secondary outcomes

2.1.4.2.1 Oncologic outcomes:

1. Cancer-related survival (C-RS)) [defined as the chance that a patient has not died of reasons related to cancer at a given time point]
2. Local recurrence-free survival (LR-FS) [defined as the chance that a patient is without local recurrence of cancer at a given time point]
3. Metastasis-free survival (M-FS) [defined as the chance that a patient is without metastasis of cancer at a given time point]

2.1.4.2.2 Surgical outcomes:

1. 30-day postoperative mortality
2. Major and minor surgical complications (using the Clavien-Dindo classification [41]: I-II=minor, III-V=major)
3. Length of hospital stay (LOS)
4. Incomplete resection/conversion rate

2.1.4.2.3 Functional outcomes:

1. Quality of life, as measured by standardized scales such as Short-Form Health Survey (SF-36, [42]) and Euro Quality of Life-5D scales (EQ-5D, [43])
2. Genitourinary function, as measured by standardized scales such as Quality of Life Questionnaire CR-29 (QLQ CR29, [44])

2.2 Search methods for identification of studies

A unique search query was designed for each database (Appendix A) according to Cochrane recommendations in the handbook and with their direct involvement. An initial search was designed and undertaken with the help and supervision of a life sciences librarian (Ms. Kathryn Hornby, Woodward Library, UBC Vancouver campus).

2.2.1 Electronic databases

We searched the following electronic databases for primary studies from 1983 onwards without any language restrictions (Table 2.1):

1. The Cochrane Central Register of Controlled Trials (CENTRAL)
2. Ovid MEDLINE
3. Ovid EMBASE
4. Science Citation Index-expanded via the Web of Science

2.2.2 Grey Literature

We searched the grey literature database OpenGrey (http://www.opengrey.eu), ProQuest dissertations and theses database (https://search.proquest.com), and ISI Conference abstracts and proceedings database (http://www.proceedings.com).

A list of the most relevant conferences to include in the grey literature search was compiled based on consulting the expert opinion of a group of colorectal surgeons. The following peer-reviewed conferences were selected based on impact within the rectal cancer literature (from 1983 to present): European Colorectal Congress; American Society of Colon and Rectal Surgeons Annual Meeting; International Society of Laparoscopic Colorectal Surgeons Congress; and Congress of Asia Pacific Federation of Coloproctology.

We also searched for relevant documents in key organizations such as the American Society of Clinical Oncology (ASCO), the American Society of Colon and Rectal Surgeons (ASCRS), the European Society of Coloproctology (ESCP), and European Society for Medical Oncology (ESMO) from 1983 onwards.

2.2.3 Hand-searching

We hand-searched reference lists of all retrieved and relevant publications identified through the above strategies. We will identify reviews, meta-analyses, and guidelines on the topic of our review and look for further relevant studies.

2.2.4 Unpublished and ongoing studies

We searched the below trial registries for unpublished and ongoing studies and contacted the authors to ask for their respective data, if relevant (strategies for ongoing trials are presented in Appendix A):

1. ClinicalTrials.gov by United States National Library of Medicine (http://www.clinicaltrials.gov)
2. International Standard Randomised Controlled Trial Number Registry (http://www.ISRCTN.com)
3. The International Clinical Trials Registry Platform by World Health Organization (http://apps.who.int/trialsearch/)
4. National Cancer Institute (NCI) Clinical Trials Registry (www.cancer.gov/clinicaltrials)

2.3 Data collection and analysis

2.3.1 Selection of studies

Two review authors (AM and NM) independently screened the title and abstracts of studies identified from the electronic, grey literature, and hand searches and determined whether a study is eligible for inclusion (see Criteria for considering studies for this review). A study flow diagram is provided to document the process (PRISMA flow chart, [45]). We retrieved the full texts of potentially eligible references for definitive assessment of eligibility. At this stage, we only excluded those studies classified by both review authors as 'exclude'. Any disagreement was resolved by discussion or by the help of the third review author (TP). We tried to obtain further information about any trial published only as an abstract. If a full report was not available or there was insufficient information to determine the eligibility of a study, we labelled them as "awaiting classification" and contacted the study authors. We summarized in a table all the relevant 'excluded' studies after the assessment of the full text with the main reason for their exclusion. The review process, including citation screening, study selection, risk of bias assessment and data extraction, was performed using the Covidence software (Covidence 2018).

2.3.2 Data extraction and management

Two reviewers (AM and NM) independently extracted data from included trials, using a piloted data extraction form (Appendix 6) based on the CONSORT statement for non-pharmacological interventions for RCTs [46]. For each included study, we attempted to obtain

the protocol of the study and extract the following characteristics to present in a table of "characteristics of included studies":

- Study title, authors, accrual dates, year of publication, journal citation
- Funding sources and conflicts of interest
- Study setting, design, single/multi-centre (and number of centres)
- Inclusion and exclusion criteria
- Number of participants randomized/assessed for each outcome
- Number of exclusions/withdrawals/missing data
- Follow-up duration
- Age, sex, and relevant baseline characteristics of participants (e.g. comorbid conditions)
- Stage of rectal cancer and tumour characteristics in intervention groups
- Intervention and control
- Co-interventions (e.g. neoadjuvant/adjuvant CRT)Outcome measures reported
- Treatment protocol and quality of intervention [47]
- Risk of bias domains

We reported the data according to the intention-to-treat principle. The review authors compared the results and resolved any disagreements by discussion until a consensus was reached. One review author (AM) automatically populated the data onto the review file in Review Manager 5.3 software using the Covidence software, and a second reviewer (NM) checked the data entry.

For surgical complications outcomes in studies before 2004 or those not using the Clavien-Dindo classification, if re-categorization and pooling such data with Clavien-Dindo grades were reasonable, we attempted to do so. Otherwise, we reported them separately.

If relevant data were not directly reported (for example HR and its 95% CI for time-to-event data, or SD for continuous data), we extracted the data required for their estimation using Parmar's methods [48-50].

2.3.3 Dealing with duplicate publications

Duplicate publications were excluded and reported in the "characteristics of excluded studies' table. When multiple reports of a particular study were identified, the study was the unit of interest for this review. We gave priority to the report with the most complete data and longest follow-up, but all reports were examined and collated in order to ensure maximum data is extracted from the study. The primary source for each study data is indicated.

2.4 Assessment of risk of bias in the included studies

Two reviewers (AM and NM) independently assessed and judged the risk of bias across the following domains based on criteria used in the Cochrane 'Risk of bias tool' (Chapter 8.5.d, [51], Appendix B):

1. Random sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?

3. Blinding (masking) of participants, personnel, and outcome assessors: Was knowledge of the allocated interventions adequately prevented during the study?
4. Incomplete outcome data: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?
6. Other problems in protocol execution or design that may affect individual outcomes reported such as:
    - Were the groups similar at baseline regarding the most important prognostic indicators?
    - Did both treatment and control arms receive treatment consistent with the standard of care for disease stage?
    - Were the cointerventions (other than CRT) within treatment arms avoided or similar?
    - Was the study apparently free of early stopping?
    - Was the study apparently free of academic bias?
    - Was the study apparently free of any source of funding bias?

Each domain was labelled as having a low, high, or unclear risk of bias. Disagreements were resolved by discussion to reach consensus and, if necessary, with the involvement of a third author (TP).

We considered domains 1, 2, 4, and 5 as 'key domains' when assessing the risk of bias for each study. For individual outcomes, other domains were also used for assessing the risk of

bias (Appendix 8). We summarized and presented the overall risk of bias for each outcome considering the assessments for its key domains in two different manners [51](Table 2.1):

1. Within each study across domains: each outcome was defined as having a "low risk of bias" only if it met all the key domains; as "high risk of bias" if it demonstrated a high risk of bias for one or more of them; or an 'unclear risk of bias' if it demonstrated unclear risk of bias for at least one key domain without any of them described as 'high risk of bias'.
2. Across studies: each outcome was defined as having a 'low risk of bias' if most information was from studies at low risk of bias; as 'high risk of bias' if the proportion of information from studies at high risk of bias was sufficient to affect the interpretation of the results; or an "unclear risk of bias" if most information was from studies at low or unclear risk of bias.

Outcome	Risk of bias domain					
	1. Random sequence generation	2. Allocation concealment	3. Blinding of participants /personnel (a)/outcome assessors (b)	4. Incomplete outcome data	5. Selective reporting	6. Other problems in protocol execution or design that may affect individual outcomes
Disease-free survival	•	•	b	•	•	•
Sphincter function	•	•	a,b	•	•	•
Oncologic outcomes	•	•	b	•	•	•
30-day postoperative mortality	•	•	b	•	•	•
Major and minor postoperative complications and Length of stay	•	•	a,b	•	•	•
Incomplete resection/conversion rate	•	•	b	•	•	•
Functional outcomes	•	•	a,b	•	•	•

Table 2.1 Key domains in assessing risk of bias for each outcome

The authors acknowledge that certain outcomes are subjective and thus affected by the lack of masking in a study (self-reported or investigator-reported outcomes, e.g. outcome 2.1.4.1.2). Subjective outcomes that were inconsistently reported were described and tabulated but excluded from statistical analysis. On the other hand, objective outcomes are less affected by lack of blinding and all data relating to these outcomes were extracted. However, studies not providing quantitative and validated measures of objective outcomes were flagged for high risk of bias.

2.5 Measures of treatment effect

The measure of treatment effect depended on the types of data presented in individual studies:

- For time-to-event data (e.g. overall survival), we used the hazard ratio (HR) and its 95% confidence interval (95%CI) where available.
- For dichotomous data (e.g. major complications), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed, in order to estimate the relative risk (RR) and its 95% CI.
- For continuous data (e.g. length of hospital stay), we calculated the mean difference (MD) with standard deviations (SD). If measures are reported using different scales (e.g. QoL), we used the standardized mean difference (SMD). When medians and interquartile range were the only data provided, the median will be used as a proxy measure of the mean and the difference between the first and third inter quartile as equivalent to 1.35 of the SD.

We used the Peto odds ratio (Peto OR) method where the event rate was <10% [48]. We reported study results with their associated 95%CI. In case of reporting P-value for outcomes, the statistical significance threshold was considered at 0.05.

2.6 Unit of analysis issues

The unit of analysis in this review is the individual patient. We will not include cluster-randomized trials or other forms of trial designs that may introduce unit-of-analysis issues.

2.7 Dealing with missing data

In the case of missing data, we attempted to contact the study authors to obtain the data and documented our attempts and their replies in the "characteristics of included studies" table. In the case of an unsuccessful attempt, we analyzed the data as reported and addressed the potential impact of the missing outcomes on the results of our review by performing a sensitivity analysis (best case/worst case analysis). We also documented the number of participants randomized and analyzed to clarify the possibility of attrition bias.

In the surgical treatment of participants with early rectal cancer, exclusion of participants after randomization is sometimes justifiable. For example, some participants admitted to the trial may have been found intra-operatively to have metastatic disease, revealing the fact that the participant was not eligible for the trial ([48, 52]. We considered this type of post-randomization exclusions as appropriate.

2.8 Assessment of heterogeneity

Where studies were considered similar enough (based on consideration of participants and interventions) to allow pooling of data using meta-analysis, we assessed the degree of heterogeneity by visual inspection of forest plots and by examining the Chi^2 test for heterogeneity. We reported our reasons for deciding that studies were similar enough to pool statistically. Heterogeneity was quantified using the I^2 statistic. An I^2 value of 50% or more was be considered to represent substantial level of heterogeneity [53], but this value was interpreted in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P-value from the Chi^2 test [48]. Where heterogeneity was present in

pooled effect estimates, we explored possible reasons for variability by conducting subgroup analysis to examine if the population, interventions and outcomes (or the way in which they are measured) differ substantially. If few trials were included in the meta-analysis, the Chi^2 test would have little power to detect heterogeneity. Therefore, we did not necessarily interpret a non-significant result as evidence of no heterogeneity but instead interpreted the findings with care.

Where we detected substantial clinical, methodological or statistical heterogeneity across included studies, we did not report the pooled results from meta-analysis but instead used a narrative approach to data synthesis. In this case, we clearly reported our reasons for deciding that studies were too dissimilar to meta-analyze. We also attempted to explore possible clinical or methodological reasons for this variation by grouping studies that were similar in terms of surgical methods, co-interventions, or other possible factors to explore differences in intervention effects.

2.9 Assessment of reporting biases

We attempted to minimize reporting bias by undertaking an extensive and exhaustive search process and by including both published and unpublished studies, and critically appraising the latter to assure they are of sufficient quality. We assessed potential publication bias for the primary outcomes with the use of funnel plots if we would identify more than 10 included studies, as recommended in chapter 10 in the Cochrane Handbook for Systematic Reviews of Interventions [51] Nevertheless, because there are several explanations for funnel plot asymmetry when assessing for small-study effect, we would interpret the findings cautiously.

2.10 Data synthesis

We performed the analyses using the Review Manager 5.3 (RevMan 2014) provided by the Cochrane Collaboration and using Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions [53] as a guide. We combined the outcome measures from individual trials in a meta-analysis to calculate a pooled effect estimate for each outcome only if the study participants, interventions, and outcomes were clinically and methodologically comparable to provide a meaningful summary. Due to the anticipated variability in the interventions of included studies, we used a random-effects model for meta-analysis [53]. We excluded all studies rated at a high risk of bias on sequence generation from the analysis and further conducted a sensitivity analysis to investigate the effects of this decision. If we were unable to pool data and perform a meta-analysis for an outcome, we reported the reasons for not doing so and instead sought to interpret the data qualitatively for the outcome in question across studies. A narrative summary of the outcome was presented in tables. Interpretations of results acknowledged and take into account the heterogeneity of the studies.

Chapter 3: Search Results

3.1 PRISMA flow-chart

The literature search found 13840 titles. After the removal of 6874 duplicates using the Covidence software, 6966 reports were screened, of which 6949 did not meet the eligibility criteria. Fourteen studies (comprised of 35 records) proceeded to full-text review, of which 6 studies (17 records) were ineligible and excluded, with reasons provided in Table 1. Five of the remaining eight studies (10 records) did not have any data available because of either being ongoing (Zhang 2018 Serra Aracil 2018 Rombouts 2017, Bach 2009) or having a mixed group of patients with no separate data available for eligible patients, marked as awaiting classification (Rullier 2017). As a result, we included three studies (comprised of eight reports) that reported outcomes on LE versus RR for early rectal cancer (Winde 1997 Lezoche 2012 Chen 2013). The PRISMA flow diagram is shown in Figure 3.1.

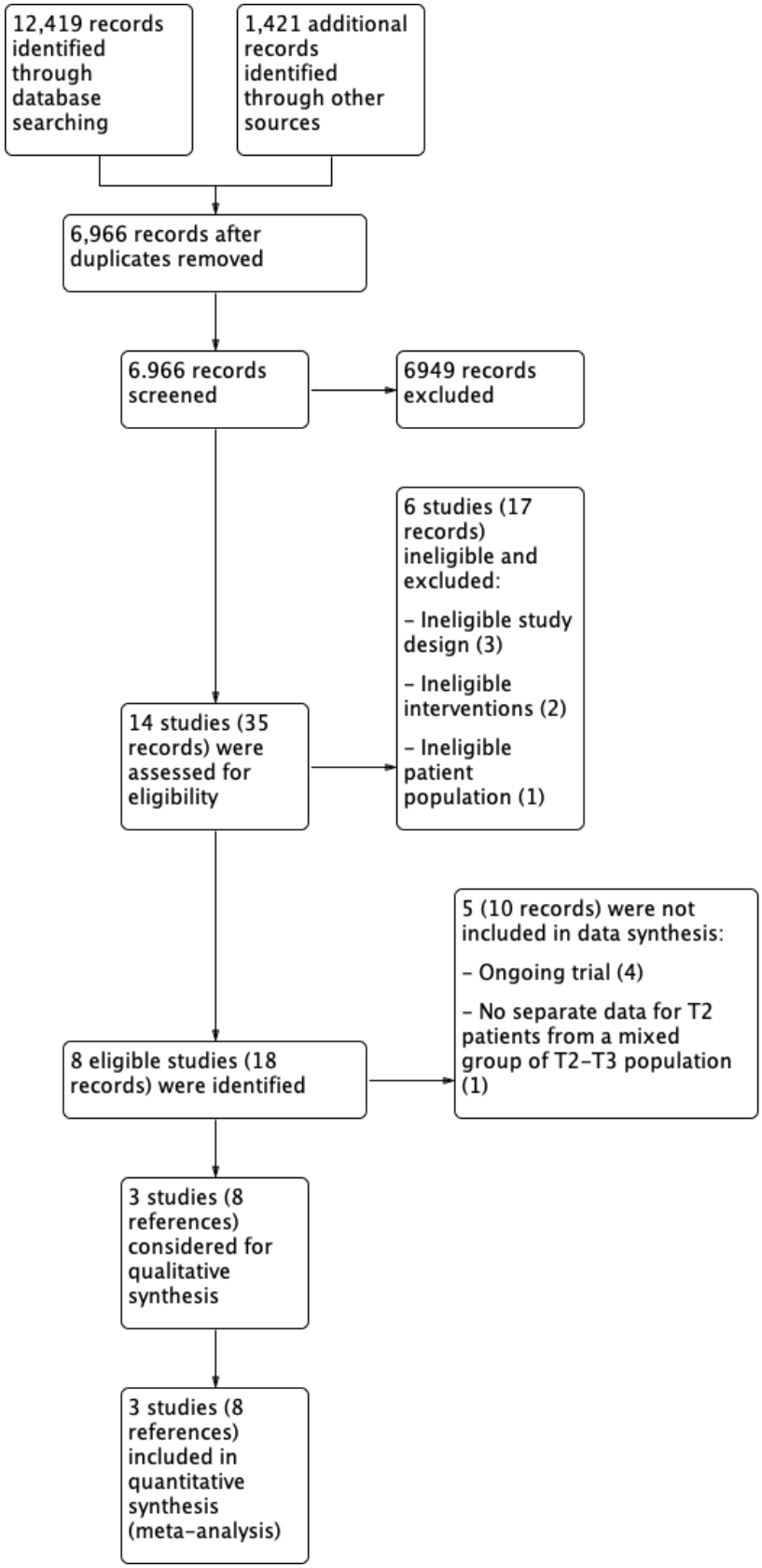

Figure 3.1 PRISMA flow diagram

3.2 Included studies

The results of this review are based on three studies (Winde 1997; Lezoche 2012; Chen 2013) published between 1997 and 2013. Overall. They collectively reported on 211 participants with T1-T2N0M0 rectal cancer undergoing local excision by TEM versus TME by open/laparoscopic LAR and APR. The duration of follow up ranged between a mean of 17 months (Chen 2013) to a median of 9.6 years (Lezoche 2012).

1. The Winde 1997 study (4 records, funding information N/A) was a parallel-design single-centre RCT of 53 participants with uT1N0M0 rectal cancer and mean age of 60.9-63.7 years enrolled from 1984 to 1992 who were randomized to TEM (n = 25) versus open anterior resection (n = 28). No CRT was used. The mean follow-up was between 40.9-45.8 months. Outcomes of interest were listed as intraoperative blood loss, operation time, time of hospitalization, early and late morbidity including local and distant recurrence, mortality, postoperative analgesia and survival probability.

Study Identification	
Sponsorship source	Not mentioned
Country	Germany
Setting	-
Comments	-
Authors name	Priv. Doz., Dr. Günther Winde
Institution	Klinik und Poliklinik fir Allgerneine Chirurgie, Westfalische Wilhelrns Universitat Monster
Email	-

Address	Waldeyerstrak 1, D-48129 Munster, Germany
Accrual dates	1984 and 1993
Citation	G. Winde, G. Blasius, R. Herwig, N. Lügering, R. Keller & R. Fischer (1997) Benefit in therapy of superficial rectal neoplasms objectivized: Transanal endoscopic microsurgery (TEM) compared to surgical standards, Minimally Invasive Therapy & Allied Technologies, 6:4,315-323, http://www.tandfonline.com/action/showCitFormats?doi=10.3109/13645709709153083
Conflict of interest	None declared
Date of Publication	1997
Funding source/sponsors	Not mentioned
Methods	
Design	Randomized controlled trial
Group	Parallel group
Follow-up duration	5 years
Number of participants	53
Single/Multi-center (number)	Single
Population	
Inclusion criteria	Low-risk rectal cancer (complete rectum) with <=4cm diameter or sessile rectal adenomas of the lower and middle rectal third, independent of morphology and dysplasia grading, confirmed histologically and by intraluminal ultrasound to TNM stage uT1 negative. Tumour location (by proctoscopy) was classified to the lower (<=8cm), middle (>8 <=12cm) and upper (>12 <=18cm) rectal third by measuring the distance from the tumour margin to the dentate line

Exclusion criteria	Strong general contraindications to surgery, or any severe infection and/or serious metabolic disorders (excluding diabetes mellitus) were defined as exclusion criteria.	
Group differences	None	
Stage of Cancer (TNM)	uT1N0M0	
	Local excision	Radical resection
Age	63.7	60.9
Gender (M: F)	0.7	1.2
Comorbid conditions	none	none
Number randomized/Number assessed	54	54
Number of exclusions/missing data	1	1
Distance of lower tumour margin from anal verge	-	-
FU (years)	10	10
Alive at follow-up	all	all
Downstaging	-	-
Interventions		
	Local excision	*Radical resection*
details	TEM was performed in the Trendelenburg lithotomy position, in Jack-knife position, or in side-positioning on the operation table. After the perianal region was prepared and draped, the anal canal was gently dilatated, and the TEM-	Open laparotomy was performed in supine position, dissection along the perirectal fascia, total mesorectal excision, ligation of the inferior mesenteric artery and mobilization of the splenic flexure if necessary. Hand-sewn straight end-to-end

	equipment, invented by Buess in 1984 (R. Wolff GmbH, Knittlingen, Germany [l]) was inserted. TEM utilized a rectoscope with 40 mm diameter and 10 or 20 cm of tube length	anastomosis (4-0 Vicryl; Ethicon, Hamburg, Germany or Maxon; Braun, Melsungen, Germany) was used. A 20 mm distal margin of the resected, not distended specimen was considered adequate for surgical safety
neo/adjuvant therapy	none	none
Intervention	TEM	LAR (TME)

Table 3.1 Details of the study by Winde

2. The Lezoche 2012 study (3 records), sponsored by the University of Roma La Sapienza, was a single-centre RCT of 100 cT2N0M0 rectal cancer patients with a median age of 66 enrolled from 1997 to 2004 who were randomized to TEM (n = 50) versus laparoscopic TME (n = 50) and received neoadjuvant long-course three-dimensional four-field chemoradiotherapy. Patients were followed for a median of 9.6 years. Median tumour distance from the anal verge was 4.92-5.0cm and the primary endpoint of the study was local recurrence or distant metastases at 5 years.

Study Identification	
Sponsorship source	University of Roma La Sapienza
Country	Italy
Setting	Single centre
Comments	none
Authors name	G. Lezoche
Institution	Department of General Surgery, University Politecnica delle Marche
Email	lezoche@me.com
Address	Department of General Surgery, University 'Politecnica delle Marche', Via Conca 71, 60126 Ancona, Italy
Accrual dates	April 1997 and April 2004
Date of Publication	April 9, 2012
Citation	DOI:10.1002/bjs.8821
Funding source/sponsors	University of Roma La Sapienza
Conflict of interest	The authors declare no conflict of interest.
Methods	
Design	Randomized controlled trial
Group	Parallel group

Single/Multi-center (number)	Multi (2)	
Number of participants	100	
Follow-up duration	Follow-up until local or distal recurrence, to a maximum of 5 years.	
Population		
Inclusion criteria	American Society of Anesthesiologists (ASA) fitness grade I–II; superior margin of the tumour located within 6 cm of anal verge; histologically-confirmed well (G1) or moderately well (G2) differentiated adenocarcinoma with a diameter no larger than 3 cm	
Exclusion criteria	Higher-risk patients (ASA III-IV) with more proximally located tumours, poorly-differentiated (G3) or undifferentiated (G4) tumours, and tumours with lymphovascular or perineural invasion	
Group differences	Patients in the two groups were similar in terms of demographic features and response to neoadjuvant treatment	
Stage of Cancer (TNM)	Stage-I: T2N0M0	
	Local excision	*Radical resection*
Age	66 (58-70)	66 (60-69)
Gender (M:F)	30:20	34:16
Comorbid conditions	--	--
Number assessed/Number randomized	50/50	50/52
Number of exclusions/missing data	2/0	2/0
Distance of lower tumour margin from anal verge	4.92 (3-6)	5.0 (3-6)
FU (years)	9.6 (8.5-11.1)	9.6 (7.4-11.9)
Alive at follow-up	40	43
Downstaging	post-neoadjuvant	reported
Interventions		

	Local excision	*Radical resection*
Neoadjuvant therapy	Both groups: Neoadjuvant chemoradiation 50.4 Gy in 28 fractions over 5 weeks with 5-FU chemo Both groups: operation performed 45-55 days after. Bowel preparation, prophylactic antibiotics preoperatively.	
Surgical intervention	TEM	LAR and APR TME

Table 3.2 Details of the study by Lezoche

3. The Chen 2013 study, funded by Shanghai Municipal Department of Health, was a parallel-design single-centre RCT of 58 participants with T1-2N0M0 rectal cancer and mean age of 66.2-68.8 years enrolled from 2008 to 2010 and were randomized to TEM (n = 28) versus laparoscopic low anterior resection (n = 30). Mean follow-up was between 17-18 months. Median tumour distance from the anal verge was between 7.8-8.1cm. The primary outcomes were defined as operative time, intraoperative blood loss, conversion rate, postoperative recovery time, surgical morbidity, mortality, local recurrence and distal metastasis.

Study Identification	
Sponsorship source	Shanghai Municipal Department of Health
Country	China
Setting	Jiading Renji Hospital
Comments	none
Authors name	Chen, Y., Liu, Z., Zhu, K., Shi, P., Yin, L.
Institution	Department of Surgery, Jiading District Central Hospital
Email	cyycx2006@yahoo.com.cn
Address	Department of General Surgery, Jiading District Central Hospital, 1 Chengbei Rd, Shanghai 201800, China
Accrual dates	January 2008 to December 2010
Citation	https://dx.doi.org/10.5754/hge12868
Conflict of interest	None declared
Date of Publication	2013
Funding source/sponsors	Shanghai Municipal Department of Health
Methods	
Design	Randomized controlled trial
Group	Parallel group
Number of participants	60

Single/Multi-center (number)	1	
Population		
Inclusion criteria	Staging: Rigid sigmoidoscopy, EUS, CT, MRI, +/- ultrasonography. T1-2 tumours Adenocarcinoma 6 to 15 cm from the anal verge Moderate to well-differentiated adenocarcinoma "acceptable physical tolerance"	
Exclusion criteria	Previous surgery Distant metastases T3 tumours or greater	
Group differences	Tumour size: LAR tumours significantly larger in size (2.3 +/- 0.5 vs. 2.8 +/- 0.6)	
Stage of Cancer (TNM)	T1-2N0M0	
	Local excision	Radical resection
Age	68.8 +/- 5.3	66.2 +/- 7.7
Gender (M:F)	14:16	17:13
Comorbid conditions	HTN, DM, CVD	-
Number assessed/number randomized	28/30	30/30
Number of exclusions/missing data	2/30	0/0
Distance of lower tumour margin from anal verge	7.8 +/- 1.6	8.1 +/- 1.3
FU (mos)	18.0 +/- 2.6	17.5 +/- 2.2
Tumour stage cT1	24/30	22/30
Tumour stage cT2	6/30	8/30
Hypertension	-	-
Tumour stage pT1	22/30	22/30
Tumour stage pT2	8/30	8/30

Interventions		
	Local excision	Radical resection
co-intervention: Neoadjuvant	none	none
co-intervention: adjuvant chemotherapy	0	8/30
Adjuvant Chemoradiation	0	0
intervention	TEM	LAR TME

Table 3.3 Details of the study by Chen

Studies differed in a number of factors including criteria for inclusion of participants, interventions, use of neoadjuvant or adjuvant CRT, follow-up investigations, and duration of follow-up:

1. Criteria used for inclusion of rectal cancer patients

All studies used the TNM staging system to identify early rectal cancer patients and excluded patients with poorly-differentiated rectal tumours. However, one study did not use pelvic MRI to stage the tumour (Winde 1997) while the other two studies (Lezoche 2012; Chen 2013) used pelvic MRI. Two studies included patients with ultrasonographic T1 (Winde 1997) or clinical T1-T2 tumours (Chen 2013); the third study included patients with T2 tumours after neoadjuvant CRT with exclusion of those with tumour progression post-CRT (Lezoche 2012).

2. Surgical technique

The technique used for TEM was similar across studies. The technique for TME was open LAR in Winde 1997, laparoscopic LAR or APR in Lezoche 2012, and laparoscopic LAR in Chen 2013.

3. Use of chemoradiotherapy

No CRT was used in Winde 1997, while all patients in Lezoche 2012 received neoadjuvant CRT as long-course three-dimensional four-field pelvic chemoradiotherapy with daily 5-fluorouracil before randomization. Chen 2013 used adjuvant chemotherapy (FOLFOX-4) in eight (of 30) patients who had high-risk tumours postoperatively.

4. Follow-up protocol

Slight differences existed between follow-up protocols to detect local or distant recurrence: Winde 1997 followed up patients by tumour markers, chest radiography, abdominal and endoluminal ultrasonography, and proctoscopy every 3 months for the first 2 years and then every 6 months for up to 5 years and annually thereafter; Lezoche 2012 followed up with tumour markers and sigmoidoscopy every 3 months for the first 3 years and every 6 months thereafter, and whole-body CT and pelvic MRI every 6 months for the first 5 years; Chen 2013 followed up with tumour markers, chest radiography, ultrasonography, colonoscopy every 6 months and abdominal/pelvic CT or MRI annually for the first 5 years.

3.3 Studies awaiting classification and ongoing studies

One study (Rullier 2017) potentially has a subgroup of eligible patients but no data became available by the time of this review and was marked as awaiting classification (Table 3.4). The following four studies were ongoing and potentially eligible (Table 3.5):

1. Bach 2009 comparing conventional TME surgery with short-course preoperative radiotherapy (SCPRT) and delayed local excision by TEM in patients with stage-I rectal cancer;
2. the three-arm STAR-TREC study (Rombouts 2017) comparing TME to LE and CRT or LE and short-course CRT in patients with mrT1-3bN0M0 rectal adenocarcinoma;
3. Serra Aracil 2018 comparing CRT plus TEM to radical surgery (TME) in patients with T2-3N0M0 rectal cancer patients; and
4. Zhang 2018 comparing LE to Miles procedure (TME) after preoperative CRT in patients with rectal cancer stage lower than cT3cN1M0.

Rullier 2017	Characteristic
Methods	• DESIGN: Randomized controlled trial • GROUP: Parallel group • FOLLOW-UP DURATION: 3 years • NUMBER OF PARTICIPANTS: 148 randomized, 145 analyzed • SINGLE/MULTI-CENTER (NUMBER): Multicentre (15 centres) • ACCRUAL DATES: 1 March 2007 to 24 September 2012 • FUNDING SOURCE: National Cancer Institute of France, Sanofi, and Roche Pharma
Participants	• INCLUSION CRITERIA: patients aged 18 years or older able to receive chemoradiotherapy and major surgery, having lower rectal infiltrating carcinoma (≤8 cm from the anal verge), greatest diameter 4 cm,

	clinically staged T2 or T3, and N0-1 (none to three nodes ≤8 mm involved) • EXCLUSION CRITERIA: metastatic disease, anal sphincter involvement, contraindication for chemotherapy, previous pelvic radiotherapy, history of other cancer and tumours presenting with major adenoma component • GROUP DIFFERENCES: two groups were balanced in terms of patient demographic characteristics, tumour characteristics, and neoadjuvant therapy • STAGE OF CANCER (TNM): **T2-3N0-1M0**
Interventions	• **LE(n = 74)**: TEM/transanal resection including full-thickness excision of the rectal wall, with a bowel margin of 1 cm, performed conventionally or with transanal endoscopic microsurgery. • **RR (N = 71)**: laparoscopic TME with sphincter preservation --- • **CRT**: 3D conformal pelvic radiotherapy delivering 50 Gy with high-energy (18 MV) photons in fractions of 2 Gy, 5 days a week over 5 weeks. Capecitabine 1600 mg/m2 per day, 5 days per week, and oxaliplatin 50 mg/m^2 per week were administered during radiotherapy
Outcomes	• Primary outcome: a composite of death, recurrence (local or distal), major surgical morbidity (grades III–V of Dindo's classification), and severe complications (definitive colostomy, anal incontinence, or impotence) at 2 years • Secondary endpoints were local recurrence, metastatic recurrence, disease-free and overall survival at 3 years, and clinical and pathological tumour response, anal incontinence, impotence
Notes	This study has a subgroup of eligible patients. Authors were contacted regarding separate data and the process of data acquisition was initiated by a bilateral contract with the authors' institution to transfer data.

Table 3.4 Characteristics of studies awaiting classification

Study	Characteristic	Description
Bach 2009	**Study name**	TREC study [Transanal endoscopic microsurgery (TEM) and Radiotherapy in Early rectal Cancer]
	Methods	Multi-centre randomized open-label phase II feasibility study
	Participants	MRI defined stage-I rectal cancer
	Interventions	• Conventional TME surgery • Short course preoperative radiotherapy (SCPRT) and delayed local excision with TEM (after an 8 to 10-week interval)
	Outcomes	Safety: • 30-day mortality • 6-month mortality • Surgical morbidity • Bowel, bladder and sexual function (measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires [EORTC QLQ] C29 and C30) Efficacy: • Histopathological assessment of tumour down-staging according to the depth of tumour invasion and the incidence of other high-risk features • Conversion rates from organ conservation to radical surgery
	Starting date	09/11/2009
	Contact information	Dr. Simon Bach The University of Birmingham Academic Department of Surgery 4th Floor, QE Hospital Edgbaston, Birmingham B15 2TH United Kingdom +44 121 371 5889 simon.bach@uhb.nhs.uk
	Notes	The author was contacted for the possibility of available data and publication date. The probable publication date is fall 2019.
Rombouts 2017	**Study name**	STAR-TREC study [STAR-TREC: can we save the rectum by watchful waiting or TransAnal microsurgery following (chemo-) radiotherapy *vs* total mesorectal excision for early rectal cancer?]
	Methods	Three-arm (1:1:1) randomization of mrT1-3bN0M0 patients to

Participants	Patients with mrT1-3bN0M0 adenocarcinoma of the rectum
Interventions	(1:1:1) to • TME surgery • CRT and TEM (in partial responders) • Short-course radiotherapy and LE (in partial responders) • TME in poor responders to CRT or RT or high-risk post-TEM
Outcomes	Safety outcomes: • Accuracy of MRI in predicting STAR-TREC eligibility • 30-day and 6-month mortality • Surgical morbidity • Rate of tumour recurrence or regrowth within the bowel wall (experimental arm) • Rate of tumour recurrence within the mesorectum (experimental arm) • Rate of distant metastases • Pelvic failure rate: expressed as a sum of the following: (1) unresectable pelvic tumour, (2) cases requiring beyond TME surgery or (3) tumour recurrence or re-growth ≤1mm from the circumferential surgical margin after TME surgery. This outcome measure will be pivotal in challenging current clinical practice and it is our intention that it becomes the primary endpoint in phase III • bowel, bladder and sexual dysfunction (baseline and 12, 24 months post-randomization). Efficacy outcomes: • The proportion of patients with/without a stoma at 30 days and 1year • Histopathological assessment of tumour downstaging following radiotherapy according to the depth of tumour invasion and the incidence of other high-risk features in comparison to non-irradiated (control) group • The proportion of patients identified by clinical and MRI assessment as suitable for active monitoring • Conversion rates from organ saving to radical surgery • Disease-free survival • Quality of life (baseline and 12, 24 months post-randomization)
Starting date	October 26, 2016

	Contact information	Dr. Simon Bach The University of Birmingham Academic Department of Surgery 4th Floor, QE Hospital Edgbaston, Birmingham, B15 2TH United Kingdom +44 121 371 5889 simon.bach@uhb.nhs.uk
	Notes	The author was contacted for the possibility of available data and publication date. The probable publication date is the summer of 2020.
Serra Aracil 2018	**Study name**	TAU-TEM study [Non-inferiority multicenter prospective randomized controlled study of rectal cancer T2-T3 (superficial) N0, M0 undergoing neoadjuvant treatment and local excision (TEM) vs total mesorectal excision (TME)]
	Methods	Prospective, multicenter, randomized controlled non-inferiority trial
	Participants	Patients with rectal adenocarcinoma less than 10 cm from the anal verge and up to 4 cm in size, staged as T2 or T3-superficial N0-M0
	Interventions	• CRT plus TEM • Radical surgery (TME)
	Outcomes	Primary: • Local recurrence Secondary: • Survival • Disease-related mortality • Quality of life
	Starting date	March 4, 2011
	Contact information	Xavier Serra-Aracil +34937231010 ext. 20009
	Notes	The author was contacted to inquire about any available data and date of publication. The attempt was unsuccessful.
Zhang 2018	**Study name**	[Comparison of Short-term Efficacy and Long-term Prognosis for Reduction Surgery and Radical Resection in Almost-cCR Rectal Cancer Patients]
	Methods	Multicentre parallel-design randomized trial
	Participants	Patients with clinical stage rectal tumour lower than cT3cN1M0
	Interventions	• Preoperative CRT + LE

	• Preoperative CRT + Miles procedure (TME)
Outcomes	Primary outcomes: • Progression-free survival of 3 years • OS at 3 years Secondary outcomes: • Carcinoembryonic antigen (CEA) • Carbohydrate antigen 19-9 （CA-199) • International Index of Erectile Function-15 • International prostate symptom score • Female sexual function index • Wexner incontinence score • QOL
Starting date	February 13, 2018
Contact information	Contact: Rui Zhang, doctor 8613898872185 zzzrrr1234@sina.com Contact: Xin Liu, master 8618900918981liuxin5626855@sina.com
Notes	The authors were contacted for possible data and data of publication. No response was received.

Table 3.5 Characteristics of ongoing studies

3.4 Excluded studies

We excluded six studies (constituting 17 records, Table 3.6), including one study because of being a single-arm trial (Ahmad 1998), two studies because of comparing traditional LE to TME (Dewey 1985) or comparing TaTME to laparoscopic TME (Pontallier 2016), one study because of studying T3-T4 rectal cancer patients (Bosset 2006), and two ongoing studies because of randomizing patients after LE to completion TME vs. observation (Deng 2018) or to completion TME vs. adjuvant CRT (Borstlap 2016).

Study	Reason for exclusion
Ahmad 1998	Ineligible study design: a single-arm trial of LE
Borstlap 2016	Ineligible study design: randomization after LE to completion TME or adjuvant CRT
Bosset 2006	Ineligible patient population: T3-T4 rectal cancer patients
Deng 2018	Ineligible study design: randomization after LE to completion TME or observation
Dewey 1985	Ineligible interventions: open transanal resection technique vs. APR
Pontallier 2016	Ineligible interventions: TaTME vs. laparoscopic TME

Table 3.6 Excluded studies and their reason for exclusion

3.5 Risk of bias

The risk of bias for each outcome across domains in each included study was assessed (Table 3.7) and judgments for each domain in each included study are presented in Figure 3.2. Across studies, oncologic outcomes, 30-day postoperative mortality, and incomplete resection/conversion rate had an "unclear" risk of bias; surgical outcomes had "high risk of bias; functional outcomes were not reported.

Outcome	Chen 2013	Lezoche 2012	Winde 1997	Across studies
1.1 Disease-free survival	High	Low	Unclear	Unclear
1.2 Sphincter function	N/A	N/A	N/A	N/A
2.1 Cancer-related survival	High	Low	Unclear	Unclear
2.2 Local recurrence-free survival	High	Low	Unclear	Unclear
2.3 Metastasis-free survival	High	Low	Unclear	Unclear
3.1 30-day mortality	High	Low	Unclear	Unclear
3.2 Major postoperative complications	High	High	High	High
3.2 Minor postoperative complications	High	High	High	High
3.3 Length of stay	High	High	High	High
3.4 Incomplete resection/conversion rate	High	Low	Low	Unclear
4.1 Quality of life	N/A	N/A	N/A	N/A
4.2 Genitounrinary function	N/A	N/A	N/A	N/A

Table 3.7 Risk of bias in included studies in each and across studies

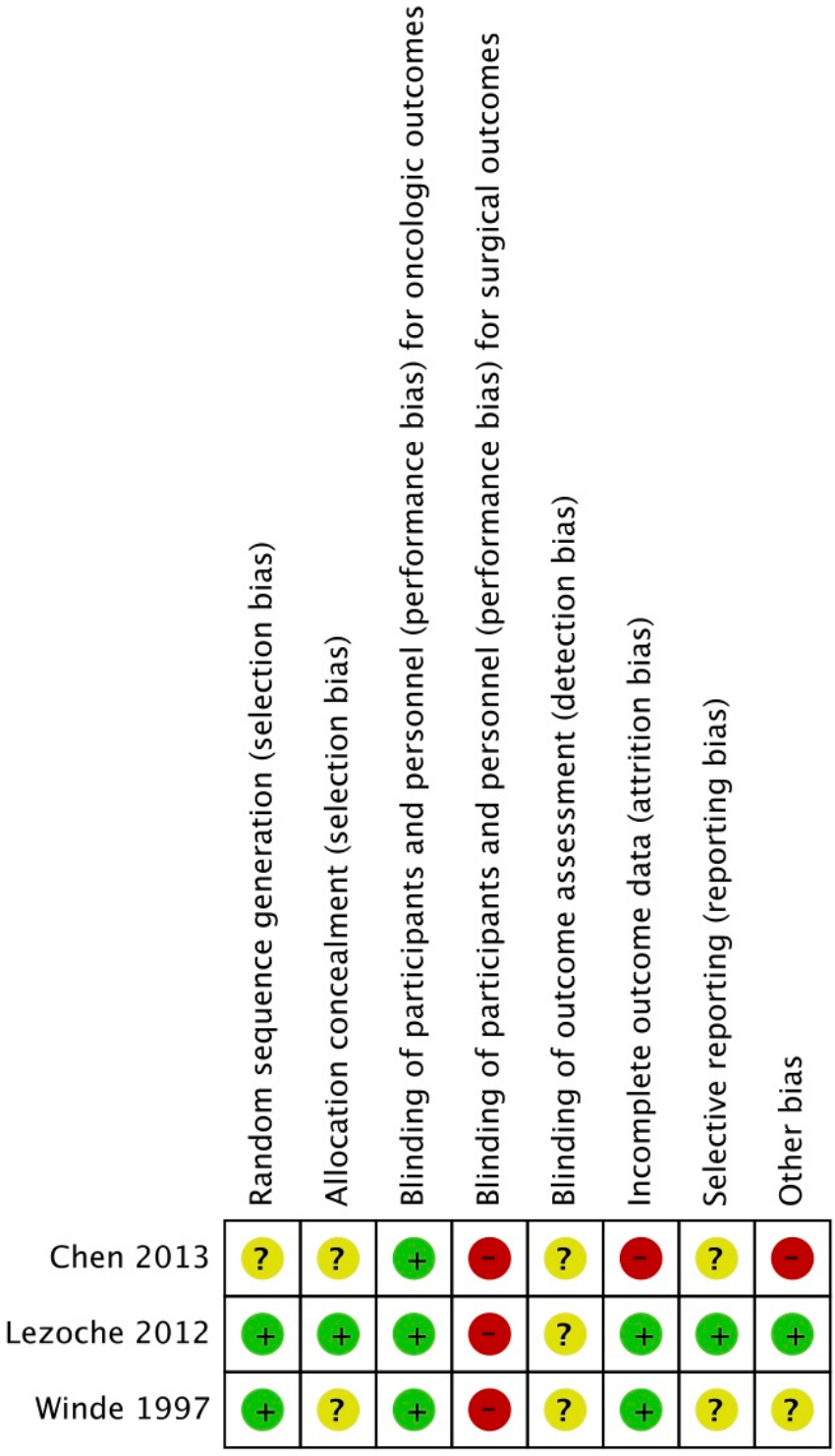

Figure 3.2 Risk of bias in each domain in included studies

? Indicates unclear risk of bias; + Indicates low risk of bias; - Indicates high risk of bias

3.5.1 Allocation and concealment (selection bias): details of random sequence generation were described in two of the three studies (Winde 1997; Lezoche 2012), which were considered at low risk of selection bias. Chen 2013 did not describe the details of randomization and was judged as at unclear risk of bias. Allocation concealment was only described in adequate detail in one study (Lezoche 2012) and was judged as at low risk, whereas the other two did not describe concealment (Winde 1997; Chen 2013) and were rated at unclear risk of bias.

3.5.2 Blinding (performance bias and detection bias): As anticipated in the protocol and due to the nature of interventions, no blinding of participants and personnel were reported in any of the trials. Hence all three were judged as being at high risk of bias. However, the impact of lack of blinding was judged depending on the outcome in each study and in the SoF table. Similarly, there was no blinding of the outcome assessors in any of the studies, which were judged as at high risk of detection bias.

3.5.3 Incomplete outcome data (attrition bias): One of the three studies (Chen 2013) was rated at high risk for attrition bias since the authors excluded from the analysis two TEM patients who had perforation and did not mention them in the results. We did not detect any attrition bias in the other two studies and rated them as at low risk of bias.

3.5.4 Selective reporting (reporting bias): The study protocol was only available for one study (Lezoche 2012), which showed satisfactory reporting of the outcomes and hence

judged as at low risk of reporting bias. Other studies did not have any protocols available and were considered at unclear risk of bias.

3.5.5 Other potential sources of bias: No other source of bias was detected in Lezoche 2012 study; however, selective use of CRT in eight RR patients postoperatively rendered Chen 2013 study at high risk of bias. Due to lack of information regarding the funding agency, Winde 1997 was judges as at unclear risk of bias.

Chapter 4: Meta-Analysis Results

Due to the inclusion of only three studies, we were not able to perform the three intended comparisons (see 2.1.3). As a result, we decided to compare the two interventions irrespective of any co-interventions but considered this as a source of heterogeneity and when grading the quality of evidence.

The source of data was from all available reports of the three studies. Some time-to-event data, however, was not readily available in the reports. We contacted the authors of included studies for separate and clarification data; however, no data could be obtained in time. When possible, outcomes were individually calculated from Kaplan-Meier curves published in the studies in conjunction with data from the text, using a data extraction sheet designed according to Tierney methods [50]. Assumptions were made with regards to timings of censored data for calculation of hazard risks due to the use of 25-, 50- and 75-month time points in the horizontal axis of the Kaplan-Meier curve in Winde 1997. Moreover, Chen 2013 did not provide a Kaplan-Meier curve, which limited the amount of retrievable data and censoring. Postoperative complications were individually examined and categorized into major (grade III or IV) or minor (grade I or II) according to the Clavien-Dindo classification [41] to be able to pool in data synthesis. Outcomes 2.1.4.1.2 and 2.1.4.2.3 were not objectively reported in any of the studies. Quality of evidence was judged according to the GRADE standards.

4.1 Primary outcomes

4.1.1 Disease-free survival (D-FS)

The proportion of disease events was 8.7% (9/103) in the LE group and 5.5% (6/108) in the RR group. Low-quality evidence suggests that LE was not associated with increased hazard of disease recurrence (studies = 3, participants = 211; HR 1.48, 95% CI 0.54 to 4.02; P = 0.45; I^2 = 0%; P = 0.60, Figure 4.1). In absolute terms, this translates into 25 more disease recurrences per 1000 patients undergoing LE compared to RR, but the true effect could lie between 26 fewer and 149 more. Raw oncologic data are tabulated in Appendix C.

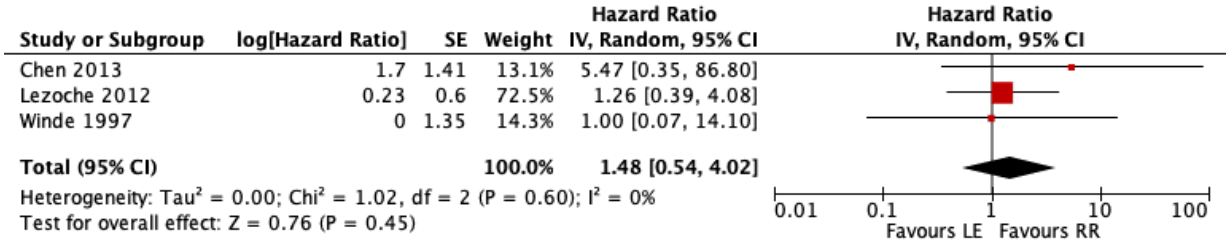

Figure 4.1 Forest plot of data for disease-free survival

In order to provide D-FS probabilities from the included studies, values were computed from the curves in each respective study (Table 4.1). According to the study by Winde, LE patients had a constant D-FS rate of 96% at 1, 3, and 5 years versus 96.2% for RR patients. In the study by Lezoche, LE patients had a D-FS rate of 90% at 1 year and 88% at 3 and 5 years, versus 100% at 1 year, 92% at 3 years, and 89.95% at 5 years for RR patients. Finally, in the

study by Chen, LE patients had a D-FS rate of 92.8% at 1 year versus 100% for the RR group. Data for 3- and 5-year follow-up was not available for the Chen study.

		Disease-free survival rates, % (N at risk)		
Study	*Group*	***1 year***	***3 years***	***5 years***
Winde	*LE*	**96**% (25)	**96**% (18)	**96**% (12)
	RR	**96.2**% (27)	**96.2**% (22)	**96.2**% (11)
Lezoche	*LE*	**90**% (50)	**88**% (45)	**88**% (43)
	RR	**100**% (50)	**92**% (49)	**89.95**% (43)
Chen	*LE*	**92.8**% (28)	*N/A*	*N/A*
	RR	**100**% (30)	*N/A*	*N/A*

Table 4.1 Disease-free survival rates of the three studies at 1, 3, and 5 years

We downgraded the quality of evidence for indirectness because of unequal use of chemoradiotherapy between the studies, which could differ from the current state of practice, as well as improved staging and detection of local and distant recurrence. We also downgraded for imprecision considering the wide 95% confidence intervals around effect estimates and the fact that only three studies with few numbers of events were used. Since there was considerable overlap in confidence intervals around the point estimates and heterogeneity was negligible (although the authors acknowledged the limitations of heterogeneity testing when the number of studies in the review is low), we did not

downgrade for inconsistency. Moreover, method of randomization was not adequately described in one of the three studies, allocation concealment was not maintained in two of the three studies, blinding of participants, personnel, and outcome assessors were not undertaken in any of the studies, and selective reporting was of unclear risk in two of the three studies. As a result, risk of bias was judged as unclear for oncologic outcomes and high for surgical outcomes. Its impact on oncologic outcomes, however, was not considered serious since they are of objective nature.

4.1.2 Sphincter function

None of the studies objectively evaluated sphincter function. Chen 2013 reported anal incontinence in three patients in the LE group and none in the RR group and "rectal pain" in 30 of 30 LE patients versus 20 of 30 patients in the RR group. Winde 1997 reported transient incontinence to stools in two LE patients versus one patient after radical resection.

4.2 Secondary outcomes

4.2.1 Cancer-related survival (C-RS)

Two of the three studies reported C-RS. Chen 2013 did not report any deaths after surgery. As a result, hazard risk was not estimable from that study. The proportion of death due to cancer was 6.6% (5/75) in the LE group and 5.1% (4/78) in the RR group. Low-quality evidence suggests that LE is not associated with increased hazard of death due to cancer (studies = 2, participants = 153; HR 1.26, 95% CI 0.36 to 4.35; P = 0.72; I2 = 0%; P = 0.84, Figure 4.2). This translates into 13 more deaths due to cancer per 1000 patients after LE,

while the true effect may be from 32 fewer to 154 more deaths. Raw oncologic data are tabulated in Appendix C.

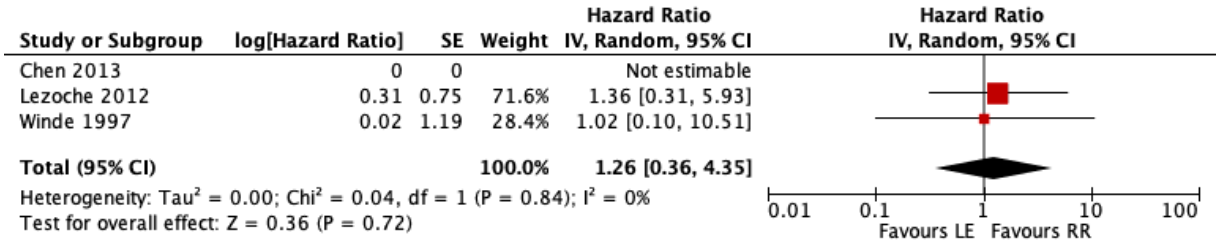

Figure 4.2 Forest plot of data for cancer-related survival

C-RS probabilities from the included studies were computed from the curves in each respective study (Table 4.2). According to the study by Winde 1997, LE patients had a C-RS rate of 100% at 1 year and 95.6% at 3 and 5 years versus a 96.2% for RR patients at 1, 3, and 5 years. In the study by Lezoche 2012, both groups had a C-RS of 100% at 1 year, 97.9% for LE at 3 years versus 98%, and a similar 93.7% at 5 years. Chen 2013 reported 100% OS/C-RS for both groups at 1 year of follow-up.

		Cancer-related survival rates, % (N at risk)		
Study	*Group*	***1 year***	***3 years***	***5 years***
Winde	*LE*	**100**% (25)	**95.6**% (18)	**95.6**% (12)
	RR	**96.2**% (27)	**96.2**% (22)	**96.2**% (11)
Lezoche	*LE*	**100**% (50)	**97.9**% (49)	**93.7**% (45)
	RR	**100**% (50)	**98**% (50)	**93.7**% (46)
Chen	*LE*	**100**% (28)	*N/A*	*N/A*
	RR	**100**% (30)	*N/A*	*N/A*

Table 4.2 Cancer-related survival rates of the three studies at 1, 3, and 5 years

Similar to the primary outcome, we downgraded the quality of evidence for indirectness because of unequal use of chemoradiotherapy between the studies, which could affect the survival rates and may defer from the current state of practice. We also downgraded for imprecision considering the wide 95% confidence intervals around effect estimates. As described earlier, we did not downgrade the quality of evidence for risk of bias since survival was an objective outcome. Similarly, heterogeneity was not considered to be of serious risk since we were expecting heterogeneity due to variability in preoperative staging work-up, surgical technique, use of chemoradiation, and slightly different follow-up diagnostic tests to diagnose recurrence. However, statistical tests could not indicate any heterogeneity and there was considerable overlap in CIs around effect estimates.

4.2.2 Local recurrence-free survival (LR-FS)

All three studies reported local recurrence after surgery. The proportion of local recurrence was 6.7% (7/103) in the LE group and 2.7% (3/108) in the RR group. After grading of the quality of evidence, low-quality evidence suggests that LE does not increase the hazard of local excision (studies = 3, participants = 211; HR 1.37, 95% CI 0.44 to 4.22; P = 0.58; I2 = 0%; P = 0.56; Figure 4.3). In absolute terms, this means 10 more recurrences per 1000 patients undergoing LE compared with RR, but the true effect may lie between 16 fewer to 84 more recurrences. Raw oncologic data are tabulated in Appendix C.

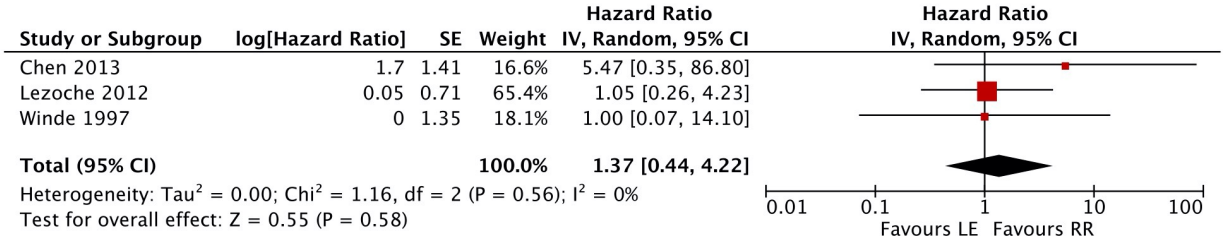

Figure 4.3 Forest plot of data for local recurrence-free survival

LR-FS probabilities from the included studies were computed from the curves in each respective study (Table 4.3). According to the study by Winde, LE patients had a LR-FS rate of 96% at 1, 3, and 5 years versus 100% for RR at those intervals. In the study by Lezoche, LE patients had a LR-FS of 92% at 1, 3, and 5 years, while RR patients were 100% local recurrence-free at 1 year, 94% at 3 years, and 92% at 5 years. Chen reported 92.8% LR-FS at 1 year for LE versus 100% for RR patients.

Study	*Group*	**Local recurrence-free survival rates, %** (N at risk)		
		1 year	***3 years***	***5 years***
Winde	*LE*	**96**% (25)	**96**% (18)	**96**% (12)
	RR	**100**% (27)	**100**% (22)	**100**% (11)
Lezoche	*LE*	**92**% (50)	**92**% (45)	**92**% (43)
	RR	**100**% (50)	**94**% (49)	**92**% (43)
Chen	*LE*	**92.8**% (28)	*N/A*	*N/A*
	RR	**100**% (30)	*N/A*	*N/A*

Table 4.3 Local recurrence-free survival rates of the three studies at 1, 3, and 5 years

We downgraded the quality of evidence for indirectness because of unequal use of chemoradiotherapy between the studies, which could affect the survival rates and may differ from the current state of practice. Of note, Chen 2013 used adjuvant CRT in high-risk RR patients (8 of 30) and reported two patients with local recurrence in the LE group during the follow-up; whereas Lezoche 2012 used neoadjuvant chemoradiation in all participants before surgery, and Winde 1997 did not use any CRT. We also downgraded for imprecision considering the wide 95% confidence intervals around effect estimates. We did not downgrade for heterogeneity or risk of bias since LR-FS was considered an objective outcome.

4.2.3 Metastasis-free survival (M-FS)

Two of the three studies reported metastasis rates. Chen 2013 did not report any metastasis during the follow-up. The proportion of patients with distant metastasis was 2.6% (2/75) in the LE group and 3.8% (3/78) in the RR group. Local excision was not associated with increased hazard of metastasis (studies = 2, participants = 153; HR 1.06, 95% CI 0.22 to 5.07; P = 0.94; I2 = 0%; P = 0.96; Figure 4.4). This means LE may result in three more metastases per 1000 patients undergoing surgery, but the true effect may lie anywhere between 29 fewer to 142 more. Raw oncologic data are tabulated in Appendix C.

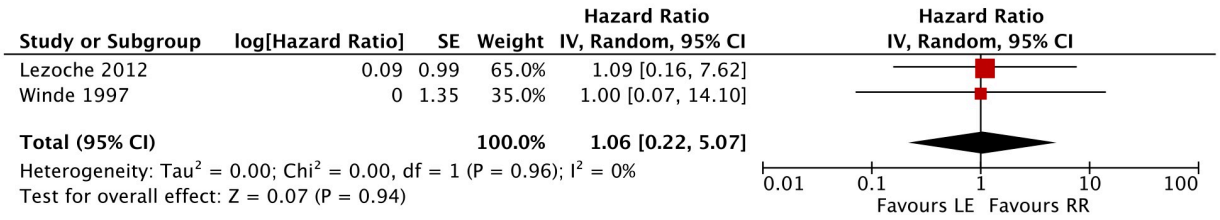

Figure 4.4 Forest plot of data for metastasis-free survival

M-FS probabilities from the included studies were computed from the curves in each respective study (Table 4.4). According to the study by Winde, LE patients did not experience any metastasis and had a M-FS rate of 100% at 1, 3, and 5 years versus 96.2% for RR at those intervals. In the study by Lezoche, LE patients had a M-FS of 97.8% at 1 year and 95.6% at 3 and 5 years, while RR patients were 100% metastasis-free at 1 and 95.6% at 3 years and5 years. Chen reported no metastasis and thus a 100% M-FS rate at 1 year for both groups.

Study	*Group*	**Metastasis-free survival rates, %** (N at risk)		
		1 year	***3 years***	***5 years***
Winde	*LE*	**100**% (25)	**100**% (18)	**100**% (12)
	RR	**96.2**% (27)	**96.2**% (22)	**96.2**% (11)
Lezoche	*LE*	**97.8**% (50)	**95.6**% (45)	**95.6**% (43)
	RR	**100**% (50)	**95.6**% (49)	**95.6**% (43)
Chen	*LE*	**100**% (28)	*N/A*	*N/A*
	RR	**100**% (30)	*N/A*	*N/A*

Table 4.4 Metastasis-free survival rates of the three studies at 1, 3, and 5 years

We downgraded the evidence for this outcome for indirectness and imprecision.

4.2.4 Surgical outcomes

4.2.4.1 30-day postoperative mortality

There were no cases of early postoperative mortality in any of the three studies.

4.2.4.2 Major and minor postoperative complications

None of the trials reported postoperative complications according to Clavien-Dindo classification [41]. Using details presented in all reports of the studies, we reviewed and

categorized complications to major (grade III-IV) or minor (I-II). The categorization of each complication in each study is presented in Table 4.5.

Study	Minor (I-II)		Major (III-IV)	
	LE	RR	LE	RR
Chen 2013	• Rectal bleeding (2) • Pneumonia (1) • Anal incontinence (3) *Total = 6*	• Rectal bleeding (3) • Rectal perforation/anastomotic leakage (2) • Pneumonia (1) *Total = 6*	-	-
Lezoche 2012	• Suture-line leakage (6) *Total = 6*	• Bleeding requiring transfusion (12) • Suture-line leakage (5) *Total = 17*	• Perianal phlegmon (1) *Total = 1*	• Anastomotic leakage (3) *Total = 3*
Winde 1997	• Disturbed micturition (2) • Transient incontinence for stools (2) *Total = 4*	• Diarrhea/constipation (5) • Disturbed micturition (2) • Transient incontinence for stools (1) • Abdominal wall hernia (1) • Rectal bleeding (1) *Total = 10*	• Rectal bleeding (1) • Leakage or suture dehiscence healed by secondary intention (1) * • Peritoneal perforation and abscess (1) • Ischemic compartment syndrome (1) *Total = 4*	• Abdominal healing by secondary intention (4) • Leakage or suture dehiscence (1) • Anastomotic stricture (1) • Small bowel obstruction (1) *Total = 7*

Categorization was performed according to the data presented in tables and texts of all reports of the included studies.

* This complication was not presented in the table of complications but was mentioned in the text of an earlier report of the same group of participants (Winde 1996).

Table 4.5 Re-classification of postoperative complications to major or minor

Chen 2013 reported no major complications after surgery in either of the groups. Rate of other complications such as rectal bleeding, rectal perforation/anastomotic leakage, pneumonia, and transient (< 5 days) anal incontinence was similar between the groups. Rectal pain was reported in all patients undergoing LE versus 20/30 of RR patients.

Lezoche 2012 reported no statistically significant differences between the groups in minor or major postoperative complications. Six patients in the LE group had anastomotic leakage that resolved with conservative measures and one patient developed a perianal phlegmon that required ileostomy. In the RR group, ten patients required intraoperative blood transfusion due to bleeding, five patients had minor anastomotic leakage, two patients had postoperative hemorrhage requiring blood transfusions, and three patients had major anastomotic leakage requiring ileostomy.

Winde 1997 reported Douglas pouch abscess, rectal bleeding, suture dehiscence healed by secondary intention, and ischemic compartment syndrome in one patient each in the LE group, as well as two patients with disturbed micturition and two with transient incontinence to stools. In the RR group, seven major complications were reported including abdominal healing by secondary intention in four and leakage/suture dehiscence requiring, anastomotic stricture, and small bowel obstruction in one patient each. Minor complications included diarrhea/constipation in five, disturbed micturition in two, transient incontinence for stools in one, abdominal wall hernia in one, and rectal bleeding in one.

4.2.4.2.1 Major postoperative complications

All three studies reported postoperative complications. There was no case of major complications in Chen 2013. The proportion of patients experiencing major postoperative complications was 4.8% (5/103) in the LE group and 9.2% (10/108) in the RR group. Very low-quality evidence suggests that LE was not associated with lower major complication rates (studies = 2, participants = 153; RR 0.56, 95% CI 0.21 to 1.51; P = 0.25; I2 = 0%; P = 0.60; Figure 4.5). While this translates into 41 fewer major complications per 1000 after LE, the true effect could lie between 74 fewer to 47 more complications. Of note and not counted as a complication, Lezoche 2012 reported 11 (22%) temporary and 12 (24%) definitive stomas necessary in the RR patients versus no patients in the LE group.

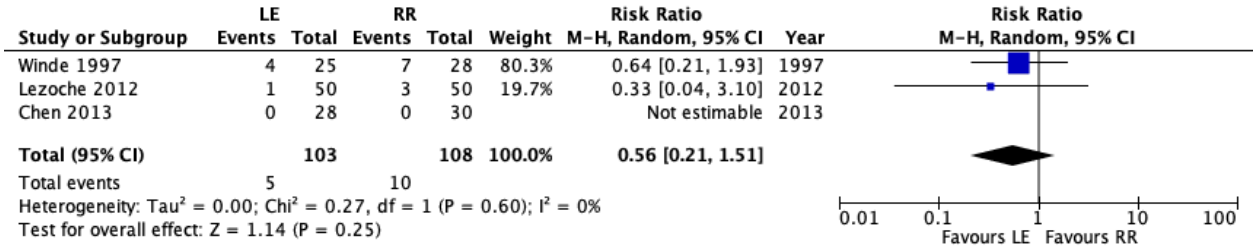

Figure 4.5 Forest plot of data for major complications

We downgraded this outcome for indirectness because of possible differences in patient populations, staging and diagnostic work-ups, surgical techniques, postoperative care protocols, and use of cointerventions. We also downgraded for imprecision considering the wide 95% confidence intervals and considering that only a few events were reported. We further downgraded the quality of evidence for high risk of bias, considering that method of randomization was not adequately described in one of the three studies, allocation

concealment was not maintained in two of the three studies, blinding of participants, personnel, and outcome assessors were not undertaken in any of the studies, and selective reporting was of unclear risk in two of the three studies. Since the heterogeneity was not detected by statistical tests and was also expected due to various differences between the trials, we did not downgrade for inconsistency.

4.2.4.2.2 Minor postoperative complications

The proportion of patients experiencing minor postoperative complications was 15.5% (16/103) in the LE group and 30.5% (33/108) in the RR group. Very low-quality evidence suggests that LE was not associated with lower minor complication rates (studies = 3, participants = 211; RR 0.53, 95% CI 0.28 to 1.03; P = 0.06; I2 = 30%; P = 0.24). This translates into 144 fewer minor complications per 1000 after LE but the true effect could lie between 220 fewer to nine more complications (Figure 4.6).

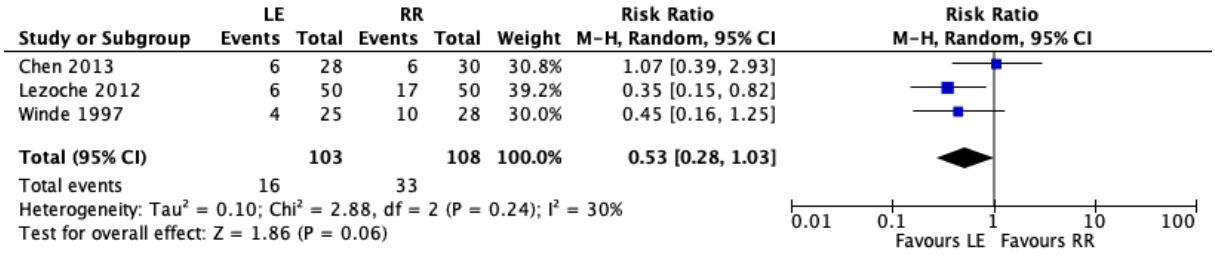

Figure 4.6 Forest plot of data for minor complications

We downgraded the quality of evidence for indirectness because of differences in patient population, staging and diagnostic work-up, surgical techniques, postoperative care

protocols, and use of cointerventions. We also downgraded for imprecision since the optimal information size criterion was not met (TSA) and the 95% CI comprises no effect. We further downgraded the quality of evidence for high risk of bias, considering that method of randomization was not adequately described in one of the three studies, allocation concealment was not maintained in two of the three studies, blinding of participants, personnel, and outcome assessors were not undertaken in any of the studies, and selective reporting was of unclear risk in two of the three studies. The heterogeneity was moderate (I^2 = 30%) but the test for heterogeneity was not significant and heterogeneity could be explained by differences between the trials regarding different factors such as staging work-up, surgeries performed, and postoperative protocols.

4.2.4.3 Length of stay (LOS)

All three trials reported length of stay. Statistical heterogeneity was very high (I^2=99%) and the test for heterogeneity was also significant (P < 0.00001) with no substantial overlap in CIs seen between the studies (Figure 4.7). While part of this heterogeneity could be anticipated due to significant improvements over time in post-operative recovery protocols and differences between the centres, as well as other differences in study populations, interventions and co-interventions, we decided not to pool the results for LOS. Furthermore, exclusion of any of the two studies at higher risk of bias (Chen 2013, Winde 1997) did not reduce heterogeneity. Two of the three trials reported shorter LOS for the LE group. For LE versus RR, Chen 2013 reported a LOS of 9.9 (SD = 2) versus 17.8 (SD = 2.3) days; Lezoche 2012 reported a LOS of 3 (SD = 0.74) versus 3 (SD = 1.48) days; and Winde 1997 reported a LOS of 5.7 (SD = 4) versus 15.4 (SD = 2) days, respectively.

4.2.4.4 Incomplete resection/conversion rate

Two of the three studies reported conversion rates. Winde 1997 did not report any patients requiring conversion. The proportion of patients requiring conversion to open was 2.5% (2/80) in the LE group and 6.2% (5/80) in the RR group. Very low-quality evidence suggests that LE was not associated with increased with increased conversion rate (studies = 2, participants = 160; RR 0.66, 95% CI 0.01 to 34.15; P = 0.84; I2 = 72%; P = 0.06; Figure 4.7). Translating to absolute terms, this meant 15 fewer conversions per 1000 patients with LE, although the true effect could be anywhere from 0 t 1000, signifying a wide confidence interval.

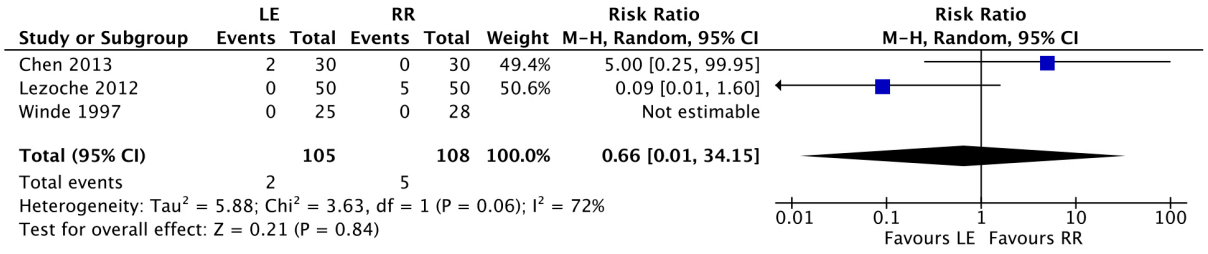

Figure 4.7 Forest plot of data for incomplete resection/conversion rate

4.2.5 Functional outcomes

4.2.5.1 Quality of life

There was no quantitative data reported for quality of life in any of the studies. Winde reported less opioid analgesic use in the LE group. Lezoche also reported a lower percentage of patients requiring analgesia in the LE group versus the RR group, 14% vs. all patients,

respectively (P<0.001); LE patients also started oral intake on the day of the operation, whereas RR patients started the liquid diet on postop day 1 or 2 and semisolid on day 3. There was only a descriptive summary of faster to getting off bed, to having bowel movements and oral intake for the LE group in the study by Chen.

4.2.5.2 Genitourinary function

Similarly, there was no qualitative evaluation of genitourinary function in any of the studies. Winde reported 2 occurrences of urinary symptoms (not explained any further) in each group. Lezcohe did not report on genitourinary function, while Chen tabulated the occurrence of rectal pain in all LE patients versus 20/30 (66.6%) in the RR group with no further explanations.

4.3 Subgroup analysis

4.3.1 Disease-free survival according to T1 vs. T2 rectal cancer

The ability to perform subgroup analysis was limited in this review by the fact that only three studies with a low number of events were included. Chen 2013 had a mixed group of T1-T2 participants and no separate data by tumour grade was available. When comparing Winde 1997, which included T1 patients, to Lezoche 2012, which included T2 patients, for the primary outcome of disease-free survival, T1 patients had a HR of 1.00 (95% CI 0.07 to

14.10) compared to T2 patients with a HR 1.26 (95% CI 0.39 to 4.08) after LE. Despite this overlap in 95% CIs of all three studies, formal subgroup analysis could not be carried out to determine the role of tumour stage.

4.3.2 Disease-free survival according to neoadjuvant versus adjuvant chemoradiotherapy

Similarly, due to the low number of studies, we were not able to undertake a subgroup analysis for the use of CRT or its type. Only Lezoche 2012 used neoadjuvant CRT in all patients. Chen 2013 used adjuvant chemotherapy selectively in eight high-risk patients after RR.

4.4 Sensitivity analysis

4.4.1 Excluding studies at high risk of bias for key domains

All three studies had at least one domain with an unclear or high risk of bias for the primary outcome. As a result and due to scarcity of the evidence, we could not determine the impact of high-risk studies. Examining the 95% CIs, however, none of the three studies were outliers and probably reflect the same true treatment effect. No leave-one-out or influence analysis could be performed.

4.4.2 Changing statistical model from random-effects to fixed-effects

Changing from a random-effects statistical model to fixed-effects did not affect the estimates, direction or magnitude of effect for the primary outcome and other oncologic outcomes. For major postoperative complications, changing to a fixed-effects model did not substantially affect the outcome, as no change was observed in the direction or magnitude of effects (Table 4.6). For minor postoperative complications, however, a change in the upper bound value of the confidence interval of the effect estimate was observed while the direction and magnitude of effect did not substantially change: RR 0.51 (95% CI 0.30 to 0.87, Table 4.6). Due to the low number of included studies, we could not vigorously evaluate the effect of study size, degree of missing data, or unpublished and low-quality studies.

Sensitivity analysis for:	Original analysis effect estimate (95% CI)	Sensitivity analysis effect estimate (95% CI)
Changing statistical model from random-effects to fixed-effects (outcome: major postoperative complications)	RR 0.56 (0.21 to 1.51)	RR 0.54 (0.20 to 1.46)
Changing statistical model from random-effects to fixed-effects (outcome: minor postoperative complications)	RR 0.53 (0.28 to 1.03)	RR 0.51 (0.30 to 0.87)

Table 4.6 Sensitivity analysis

Chapter 5: Summary of findings and quality of evidence

Overall, low quality, insufficient (TSA) evidence suggested that LE could have similar disease-free survival in patients with stage-I rectal cancer compared with RR. This non-inferiority was also suggested regarding cancer-related survival, local recurrence-free survival, and metastasis-free survival. Very low-quality evidence suggested that LE has the same postoperative safety profile in terms of major and minor complications, although available data tended to favour LE for minor complications. A major lack of evidence existed with regards to sphincter, genitourinary function and quality of life, all proposed advantages of local less traumatic excision techniques. See Table 5.1 for a full summary of findings.

Local excision compared to Radical resection for early rectal cancer with or without neoadjuvant or adjuvant therapy						
Patient or population: early rectal cancer with or without neoadjuvant or adjuvant therapy **Setting:** Tertiary care hospitals **Intervention:** Local excision **Comparison:** Radical resection						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with Radical resection	**Risk with Local excision**				
Disease-free survival (D-FS) follow up: range 17 months to 9.6 years	923 per 1,000	888 per 1,000 (725 to 958)	HR 1.48 (0.54 to 4.02)	211 (3 RCTs)	⨁⨁⊖⊖ LOW [1 2 3 4]	Absolute effects calculated based on Ptok 2007 (at 5 years)
Sphincter function	-	see comment	-	-	-	None of the studies objectively evaluated sphincter function. Chen 2013 reported anal incontinence in three patients in the LE group and none in the RR group and "rectal pain" in 30/30 LE patients versus 20/30 radical resection patients. Winde 1997 reported transient incontinence to stools in two LE patients versus one after radical resection.
Cancer-related survival (C-RS) follow up: range 17 months to 9.6 years	984 per 1,000	980 per 1,000 (932 to 994)	HR 1.26 (0.36 to 4.35)	153 (2 RCTs)	⨁⨁⊖⊖ LOW [1 2 3 4]	Absolute effects calculated based on Cao 2018 (at 5 years)
Local recurrence-free survival (LR-FS) follow up: range 17 months to 9.6 years	980 per 1,000	973 per 1,000 (918 to 991)	HR 1.37 (0.44 to 4.22)	211 (3 RCTs)	⨁⨁⊖⊖ LOW [1 2 3 4]	Absolute effects calculated based on Ptok 2007 (at 5 years)

Metastasis-free survival (M-FS) follow up: range 17 months to 9.6 years	960 per 1,000	958 per 1,000 (813 to 991)	HR 1.06 (0.22 to 5.07)	153 (2 RCTs)	⨁⨁⊖⊖ LOW [1 2 3 4]	Absolute effects calculated based on Ptok 2007 (at 3 years)
30-day postoperative mortality	Study population		-	211 (3 RCTs)	⨁⨁⨁⊖ MODERATE [1 3 4]	
	see comment	see comment				
Major postoperative complications (C-D grade III-IV) assessed with: Clavien-Dindo classification	93 per 1,000	52 per 1,000 (19 to 140)	RR 0.56 (0.21 to 1.51)	211 (3 RCTs)	⨁⊖⊖⊖ VERY LOW [2 3 4]	
Minor postoperative complications (C-D grade I-II) assessed with: Clavien-Dindo classification	306 per 1,000	162 per 1,000 (86 to 315)	RR 0.53 (0.28 to 1.03)	211 (3 RCTs)	⨁⊖⊖⊖ VERY LOW [2 3 4 5]	
Length of stay (LOS)	Winde 1997 reported a LOS of 5.7 (SD = 4) for LE versus 15.4 (SD = 2) days for RR; Lezoche 2012 reported a LOS of 3 (SD = 0.74) for LE versus 6 (SD = 1.48) days for RR; Chen 2013 reported a LOS of 9.9 (SD = 2) for LE versus 17.8 (SD = 2.3) days for RR			211 (3 RCTs)	⨁⊖⊖⊖ VERY LOW [2 3 4 6]	Due to very high statistical heterogeneity (I^2= 98%, P < 0.00001), we did not pool this outcome.
Incomplete resection/conversion rate	46 per 1,000	31 per 1,000 (0 to 1,000)	RR 0.66 (0.01 to 34.15)	160 (2 RCTs)	⨁⊖⊖⊖ VERY LOW [2 3 4 7]	
Quality of life	-	see comment	-	-	-	None of the studies evaluated quality of life in any of the patients. Chen 2013 reported significantly shorter

						postoperative period to oral intake, bowel movement, and off-bed activities in LE patients.
Genitourinary function	-	see comment	-	-	-	None of the studies reported any objective genitourinary function. Winde 1997 reported "disturbed micturition" in two patients in each surgery group.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio; **LE:** local excision

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 There was considerable overlap in confidence intervals around the point estimates and statistical heterogeneity was negligible. As a result, we did not downgrade for inconsistency. The authors acknowledged the limitations of heterogeneity testing when the number of studies in the review is low.
2 We downgraded by one level for indirectness because there was a variety in the use of co-interventions (chemoradiotherapy was used as neoadjuvant in one study, as adjuvant selectively only in one group in another study and none in the third study), which could affect both the oncologic outcomes and surgical outcomes. Moreover, the patient population in these trials might differ from the present patients due to more accurate staging of rectal cancer, use of up to date chemoradiotherapy, and better detection of disease recurrence or metastasis.
3 We downgraded for imprecision considering the wide 95% confidence intervals around effect estimates and the fact that only three studies with few numbers of events are used in data synthesis. The optimal information size criterion according to TSA was not met.
4 Method of randomization was not adequately described in one of the three studies, allocation concealment was not maintained in two of the three studies, blinding of participants, personnel, and outcome assessors were not undertaken or reported in any of the studies, and selective reporting was of unclear risk in two of the three studies. As a result, risk of bias was judged as unclear overall for oncologic outcomes and high for surgical outcomes. Its impact on oncologic outcomes was not considered serious while we downgraded the quality of surgical outcomes (except mortality and conversion rate) due to high risk of bias by one level.

5 Heterogeneity was moderate (I2= 31%) and could be anticipated due to differences in patient population, surgeries performed, or co-interventions. However, since there was considerable overlap in CIs and the test for heterogeneity was not significant (P = 0.24), we did not downgrade for inconsistency.
6 Heterogeneity was high and significant (I2= 98%, P < 0.00001) and could only partly be explained by clinical and methodological differences. As a result, we did not pool the results and downgraded for inconsistency.
7 Heterogeneity was substantial (I2=72%) between the studies with a significant test (P = 0.06). While this was anticipated due to different factors between the studies such as staging work-up, severity of disease in participants, surgeries performed, use of chemoradiotherapy, and follow-up protocols, we judged that the impact of this inconsistency was serious on the quality of evidence.

Table 5.1 Summary of findings table for all outcomes

5.1 Quality of the evidence

We graded the quality of evidence using the GRADE approach, which takes into account the risk of bias in included studies, inconsistency, indirectness, imprecision, publication bias, observing a large effect, plausible confounding, and dose-response gradient.

For evaluating risk of bias, one of the trials was at unclear risk of selection bias and two trials at unclear risk of allocation concealment. Blinding of participants, personnel, and outcome assessors was not undertaken in any of the trials. This was however not judged as having a serious impact on the outcome since blinding was not possible for these interventions. As for the other domains, attrition bias was detected in one of the trials and incomplete reporting was at unclear risk in two of the studies. Risk of bias, however, was judged to only affect the surgical outcomes with more subjective nature but not objective oncologic outcomes or mortality and conversion rates. As a result, major and minor postoperative complications and length of stay were downgraded for serious risk of bias.

For inconsistency, we evaluated the degree of overlap of 95% CIs for each outcome alongside heterogeneity testing to judge a serious impact on the certainty of evidence. For minor complications, heterogeneity was moderate (I^2= 31%) and could be anticipated due to differences in patient population and their disease severity, surgeries performed, as well as co-interventions. However, since there was considerable overlap in CIs and the test for heterogeneity was not significant (P = 0.24), we did not downgrade for inconsistency. For length of stay, despite heterogeneity was anticipated due to possible improvements over time in post-operative recovery protocols, study participants, interventions and co-interventions, we detected very high statistical heterogeneity (I^2= 99%, P < 0.00001) that could not be

explained. No substantial overlap in 95% CIs was seen between the studies. As a result, we did not pool this outcome.

For indirectness, we judged the applicability to be limited and of serious impact on the quality since the early rectal cancer patient at the present day may differ in terms of having a better staging work-up with the use of modern imaging, receiving neoadjuvant/adjuvant therapy, using laparoscopic TME or TaTME, and having better detection of disease recurrence or metastasis with current follow-up protocols. Patients in the included studies were at variable severities of stage-I rectal cancer and varied in receiving chemoradiotherapy. We were not able to investigate the effect of these differences by subgroup analyses.

Similarly, we downgraded for imprecision considering the wide 95% confidence intervals around effect estimates and the fact that only three studies with few numbers of events were used in data synthesis.

We did not judge the effect of publication bias and other confounding to be of serious impact on the quality of evidence.

Chapter 6: Discussion

We presented current evidence and assessed the oncologic efficacy and safety of modern endoscopic local excision techniques in comparison to radical resection with standard TME surgery. We identified three published RCTs alongside multiple unpublished ongoing studies that can contribute data to answer this clinical question. Considering the low quality of evidence presented in this review, an update of this study is needed that will include new information as it becomes available.

As modern endoscopic local excision techniques continue to gain popularity and expand their application, high-quality research is essential to compare their oncologic and operative advantages and pitfalls. This review found limited evidence of generally low quality supporting their role in the treatment of early rectal cancer that is confined to the rectal wall not invading beyond the muscular layer. There are some considerations regarding the applicability of these conclusions.

Firstly, while there is generally a consensus [54] that low-risk favourable T1 tumours (well- or moderately- differentiated, submucosal invasion grade 1 with no venous or lymphatic invasion or other adverse features, (Kikuchi et al., 1995)[55] could be sufficiently treated with a high-accuracy local excision technique such as TEM due to high success rates [39], role of LE for higher-grade T1 or T2 tumours remains to be defined. However, TEM in patients with higher grade tumours who are otherwise unfit for radical surgery has been used in investigational settings and shown merit especially when using chemoradiotherapy or adjuvant therapy in compassionate. We were unable to find enough evidence to perform a subgroup analysis for T1 versus T2 tumours or for use of chemoradiotherapy.

Secondly, the role of chemoradiotherapy remains to be defined in relation to local excision, as this review found only one randomized trial with low risk of bias (Lezoche 2012) that used neoadjuvant CRT in T2 patients and found comparable disease-free survivals of 88% for LE and 90% for RR during the follow-up of up to 10 years. Multiple studies from proponents of organ preservation also support this approach when good follow-up surveillance is feasible in high-risk T1, T2, and even T3N0 tumours with reported recurrence rates below 10% and disease-free survival rates around 90% [56-58]. A meta-analysis of neoadjuvant CRT + TEM suggested similar oncologic outcomes to TME in T2N0M0 patients [59]. This approach has its own limitations including the possibility of over-treatment of patients and exposing them to CRT toxicity or multiple procedures [60, 61]. This approach may thus not be advisable in good surgical candidates at least until we have stronger proof of oncologic efficacy and proven functional superiority of LE. Currently and under research protocols, such approach may be limited to good responders after neoadjuvant CRT, with completion/salvage TME in poor responders. Several ongoing RCTs are designed to investigate the role of TEM after neoadjuvant CRT [62-65]. We were not able to perform a subgroup analysis based on neo/adjuvant CRT due to the limited available evidence.

Lastly, the use of adjuvant CRT or radiotherapy after LE in high-risk tumours may be another organ-preserving alternative. An analysis of 3786 patients from the surveillance, epidemiology, and end result registry (SEER) database suggested similar 5-year cancer-specific and overall survivals rate for LE + adjuvant radiotherapy versus TME in patients with T2 rectal cancer [66]. A similar analysis by Olsheski in 2013 also found similar oncologic outcomes for stage-I rectal cancer patients undergoing LE + radiotherapy versus APR [67]. Individual experiences have also been reported for this approach, with 3-year local

recurrence of 6.9% for high-risk T1 tumours offered adjuvant radiotherapy [68] and 5-year disease-free survival of 89.8% for high-risk T1 and T2 patients offered adjuvant chemoradiotherapy [69]. Further trials are necessary to answer this question.

Regarding morbidity, this review found very low-quality evidence suggesting similar morbidity after the two approaches. Winde 1997 mostly contributed to major postoperative complication rate, which could reflect the initial technical challenges of TEM and the open approach for RR. Lezoche 2012, the highest quality RCT available to date, reported only one major complication after LE and three after RR. There was a trend towards lower minor complications after LE. All three included studies reported comparable complication rates after the two approaches while generally suggesting better recovery for LE. Current evidence supports lower morbidity rates for LE [16, 70], while more robust data is pending.

Better sphincter function, quality of life, and genitourinary function are assumed advantages of LE; yet evidence to support this claim is scarce. Doornebosch reported similar quality of life after TEM versus TME while sphincter function for TEM patients was superior [71]. Similarly, D'Ambrosio reported better QoL at 6 months after the endoluminal excision of T2-T3 cancer compared with TME, whereas at 1 year, an advantage for LE remained regarding sphincter function [72].

6.1 Potential biases in the review process

We tried to minimize the bias by following a comprehensive search strategy for electronic databases. We further searched the trial registries for ongoing trials, theses and proceedings

databases, and publications of most relevant surgical and oncological associations. We contacted the authors of eligible studies for clarification and any possible data on the missing items. The review process involved two independent authors at all stages of screening and study selection, quality appraisal, and data extraction. Data entry and analyses were done by one review author and rechecked by an adjudicating author as well as a biostatistician.

A major limitation of this study is the small number of included studies that portends a type 2 statistical error for a negative study. As well, despite contacting the authors of studies, some issues remained obscure and required assumptions to be made. These include an assumption of censoring times in Winde 1997 and timings of recurrence and metastasis in Lezoche 2012. Moreover, we were not able to obtain separate data for the eligible patients in the Rullier-2017 study, as well as any of the ongoing unpublished studies. Last but not least, an inherent bias could be introduced using indirect methods to estimate hazard ratio limits and standard errors since they were not reported and had to be calculated.

6.2 Agreements and disagreements with other studies or reviews

We found a number of reviews comparing local excision to radical resection. These reviews differed from the current review with regards to their inclusion and exclusion criteria and the type of studies included, methodology of review and search strategy, and focus of the review. All of these trials included both RCTs and observational studies.

Sgourakis and Sajid compared TEM to radical resection in T1 and T2 rectal cancer. Sgourakis included 11 studies comparing any method of LE, including traditional LE, to radical resection, and concluded that LE is superior regarding complications but inferior

regarding oncologic outcomes to RR. The authors also reported better outcomes with TEM compared to traditional open LE, but still worse outcomes for disease recurrence [70]. Sajid included 10 studies comparing TEM to RR and reported reduced risk of postoperative complications but worse recurrence with TEM [73].

Kidane and Lu compared LE to radical resection for T1 rectal cancer. Kidane included 13 studies and concluded that LE does not offer comparable oncologic control to radical surgery while offering lower postoperative complications, mortality, and the need for a permanent stoma. They also suggest that TEM may have similar oncologic efficacy to RR [74]. Lu drew from 7 studies and suggested that for patients with T1 rectal cancer, the distant metastasis, overall survival and disease-free survival rates were similar between TEM and TME, although the local recurrence rate after TEM was higher [75].

Xu considered this comparison in T2 rectal cancer patients with or without the use of neoadjuvant therapy [59]. They evaluated one RCT and three non-randomized trials and concluded that neoadjuvant therapy combined with TEM could offer similar oncologic outcomes; TEM without CRT, however, is inferior and not recommended in T2 rectal cancer. Shaikh included eight studies and compared LE to RR in any T stage rectal cancer after [36]. The authors reported similar overall survival and disease-free survival even for T3 rectal tumours.

6.3 Review of observational studies

Observational evidence on the comparison of LE versus RR for early rectal cancer is more abundant than RCTs. Table 6.1 summarizes the most significant studies done to date on this subject.

Langer in 2003 retrospectively compared patients with adenoma or early T1 carcinoma who underwent either radical surgery, Park's resection, or TEM using electrosurgery or UltraCision [76]. There was one mortality in the radical surgery group, and the mortality rate was highest within this group, followed by Park's group and TEM. The authors reported a high rate of recurrence at 2 years with Park's resection, 26%, whereas RS had only 3.7% and TEM 8.9% recurrence rates.

Lee et al. in 2003 compared patients with T1-2N0M0 rectal adenocarcinoma who underwent RR or TEM for up to 5 years [77]. The authors reported comparable recurrence rates for T1 tumours in either group, while for T2 tumours, TEM had a significantly higher recurrence rate.

Folkesson 2007 was a population-based report of 5-year outcomes after LE, consisting of TEM and other older methods, versus radical techniques such as LAR, APR, and Hartmann's [78]. LE showed fewer complications after surgery compared to all other RR techniques. Oncologically, LE was comparable to RR for stage-I rectal cancer in terms of cancer-specific survival. Overall survival was, however, worse with LE, which the authors attributed to higher comorbidities in the LE group.

Ptok 2007 was a multi-centric chart review of 479 patients who underwent RR or local excision by TEM or conventional method (majority of LE patients). After a follow-up of 5

years, LE patients showed a lower general and disease-specific complication rate, but marginally higher local recurrence rates at 5 years. However, the rates were generally low at 6 vs. 2% for LE and RR respectively [79].

Palma in 2009 compared 17 patients with early T1 rectal cancer undergoing RR to 34 patients undergoing TEM after 93 months of follow-up [80]. The authors reported significantly better operative and surgical outcomes for TEM, as well as lower complication rates. There were no cases of recurrence after RR but 2 patients in the TEM group, which did not statistical significance.

Qiu in 2012 reported their experience with TEM [81]. They compared patients with early rectal cancer undergoing TEM to RR and reported better safety and operative profile for TEM. After 3 years of follow-up for TEM patients, there was no difference in terms of disease recurrence between the two groups.

Elmessiry in 2014 reported 3-year results of RR versus LE by TEM or TAE in patients with T1-2N0M0 rectal cancer [82]. LE group had better operative outcomes and complication rates. In terms of oncological outcomes, estimated 3-year disease-free survival was comparable between the two groups for T1 tumours but not T2 tumours. When comparing TAE to TEM, no statistical difference was observed in oncologic outcomes, but a trend was seen in favour of TEM.

Cao and colleagues evaluated the Surveillance, Epidemiology, and End Results (SEER) database for both T1 colon and rectal cancer patients undergoing local versus radical resection [83]. They matched the patients in two groups using propensity scoring. They found that at 5 and 10 years, patients with T1 rectal cancer patients had similar cancer-specific

survival after either procedure and that LE did not negatively affect survival outcomes in this group of patients.

Study	Follow-up	Patients	Groups (n)	Specific outcomes	Oncologic outcomes
Langer 2003	2 years	rectal adenoma or early low-risk carcinoma (pT1, G1/2, L0)	LAR/APR (27) Park's method (76) TEM-electrosurgery (45) TEM-UltraCision (34)	Longer LOS/ one death	3.7% recurrence 26.3% recurrence* 8.9% recurrence
Lee 2003	5 years	T1-2N0M0	Radical surgery (100) TEM (74)	48% complication rate 4.1% complication rate	0% for T1, and 9.4% for T2 4.1% for T1, 19.5% for T2* Similar D-FS rates
Folkesson 2007	5 years	Stage-I rectal cancer	Local excision (643) LAR (4673)	11.5% complication rate 35.4% complication rate	95.3% D-FS for stage-I 94.5% D-FS for stage-I
Ptok 2007	5 years	pT1 rectal cancer	RR (359) TEM+LE (120)	22.8% complication rate 9.2% complication rate	2.0% recurrence 6.0% recurrence*
Palma 2009	7.5 years	T1 low-risk carcinomas	RR (17) TEM (34)	23.5% major complication 2.9% major complication	0% local recurrence 5.88% local recurrence

Qiu 2012	Median 3 years	Early rectal cancer	RR (26) TEM (21)	Shorter hospital stay, less operative blood loss, faster recovery for TEM	96.3% survival 94.8% survival
Elmessiry 2014	Median 3 years	T1-2N0M0 rectal cancer	RR (79) LE (74)	Better operative and functional outcomes with LE	94.9% D-FS T1, 87.5% T2* 84.2% D-FS T1, 61.5% T2
Stornes 2016	5 years	T1-2 rectal cancer	TME (2,042) TEM (94)	-	98.2% T1, 93.9% T2* 96.8% T1, 65.4% T2 relative survival LR rates higher for TEM*
Cao 2018	Up to 10 years	T1 colon or rectal cancer	RR (571) LE (313)	-	98.4% 5-yr, 96.7% 10-C-RS 96.6% 5-yr, 92.8% 10-C-RS

APR, abdominoperineal resection; C-RS, cancer-related survival; D-FS, disease-free survival; LAR, low anterior resection; LE, local excision; LOS, length of stay; RR, radical resection; TEM, transanal endoscopic microsurgery.

* Denotes statistically different

Table 6.1 Summary of prominent observational studies comparing local excision (LE) to radical resection (RR)

Chapter 7: Conclusion

7.1 Implications for practice

We found low-quality evidence from three randomized studies that LE by modern endoscopic techniques is comparable to RR in terms of disease-free survival, cancer-related survival, local recurrence-free survival, and metastasis-free survival. The quality of evidence was downgraded for indirectness and imprecision because the current clinical setting may offer earlier and more accurate detection, treatment, and follow-up of patients with early rectal cancer. In addition, the wide confidence intervals without any observed large effects reflect the imprecision in these effect estimates.

For surgical outcomes, no early mortality was reported by any of the approaches. Due to a lack of unified outcome reporting for surgical complications, we categorized them according to Clavien-Dindo classification[41] to be able to pool their effect estimates. This process exposed the anticipated heterogeneity between the studies in terms of study populations, interventions and co-interventions, and post-operative recovery protocols, among others. As a result, the outcomes of major and minor postoperative complications and length of stay were judged to be of very low quality, which suggested that there is no significant difference between the two approaches. This review, however, was unable to draw any conclusions about these two interventions regarding multiple suggested advantages of LE such as sphincter function preservation, quality of life after surgery, and genitourinary function.

7.2 Implications for research

Considering the results of this review, there are multiple implications for research:

- Patient selection: There are two distinct circumstances under which LE would be indicated. One, as the focus of this review, is in newly diagnosed patients with early rectal cancer who have an option to undergo RR. As suggested by this review, evidence is unable to confidently answer this question and more trials are needed in this regard. Second, in a patient unwilling to undergo or unfit for RR, LE may be used to excise a small lesion. This scenario may also apply to patients with more advanced stages of cancer, who would require a form of adjuvant therapy, most commonly neoadjuvant CRT. As suggested by Shaikh 2015, this approach may prove to be an effective and safe alternative to radical surgery.
- Defining the role of neoadjuvant or adjuvant chemoradiotherapy: Application of neoadjuvant CRT could potentially expand the indications of LE by downstaging the tumour and treating a possible spread of the tumour to surrounding tissues. As demonstrated by Lezoche 2012, a patient with a clinically node-negative T2 tumour undergoing LE after CRT would have the same disease-free survival to a similar patient undergoing RR, at a follow-up of to 10 years. A multi-centre trial in the UK is underway (Bach 2009) to compare patients with stage-I rectal cancer undergoing TME to those receiving short-course preoperative radiotherapy followed by TEM after 8-10 weeks. The strategy of neoadjuvant radiation to downstage the tumour followed by TEM is also being investigated for higher-stage tumours, with the possible outcome that LE would be an option in good and complete responders to

neoadjuvant treatment. The multi-centre STAR-TREC study (Rombouts 2017) has suggested a maximal organ-preserving strategy and aims to evaluate patients with T1-T3bN0M0 rectal cancer following randomization to three possible arms: TME surgery, neoadjuvant CRT and LE in good responders but an incomplete clinical response, short-course radiotherapy and LE in good responders but incomplete clinical response; TME would be offered to any poor responder. Serra Aracil 2018 aims to compare neoadjuvant CRT followed by LE to TME in patients with T2-3N0M0 rectal cancer patients. These studies would provide more insight into the extent to which we can expand the application of LE for the treatment of rectal cancer.

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Appendices

Appendix A- Search queries for the included databases

Database	Strategy
The Cochrane Central Register of Controlled Trials (CENTRAL)	#1 MeSH descriptor: [Rectal Neoplasms] explode all trees #2 ((rect* or anal* or anus*) near/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*)):ti,ab,kw #3 (#1 or #2) #4 MeSH descriptor: [Colorectal Surgery] explode all trees #5 (protectom* or Mason or Kraske or TEM or TEMS or Miles or Hartmann):ti,ab,kw #6 ((open or radical or local) near/3 (surgery or resection or treatment or management or excision or intervention)):ti,ab,kw #7 ((rect* or anal* or anus* or endoscopic or micro or anterior or abdominal perineal or transanal) near/3 (resection or surgery or microsurgery)):ti,ab,kw #8 (#4 or #5 or #6 or #7) #9 (#3 and #8)
MEDLINE search strategy	1. exp Rectal Neoplasms/ 2. ((rect* or anal* or anus*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*)).mp. 3. 1 or 2 4. exp Colorectal Surgery/

	5. (protectom* or Mason or Kraske or TEM or TEMS or Miles or Hartmann).mp. 6. ((open or radical or local) adj (surgery or resection or treatment or management or excision or intervention)).mp. 7. ((rect* or anal* or anus* or endoscopic or micro or anterior or abdominal perineal or transanal) adj (resection or surgery or microsurgery)).mp. 8. 4 or 5 or 6 or 7 9. 3 and 8 10. randomized controlled trial.pt. 11. controlled clinical trial.pt. 12. randomized.ab. 13. placebo.ab. 14. clinical trials as topic.sh. 15. randomly.ab. 16. trial.ti. 17. 10 or 11 or 12 or 13 or 14 or 15 or 16 18. exp animals/ not humans.sh. 19. 17 not 18 20. 9 and 19
EMBASE search strategy	1. rectum tumor/ 2. ((rect* or anal* or anus*) adj (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*)).mp.

	3. 1 or 2 4. rectum surgery/ 5. (protectom* or Mason or Kraske or TEM or TEMS or Miles or Hartmann).mp. 6. ((open or radical or local) adj (surgery or resection or treatment or management or excision or intervention)).mp. 7. 4 or 5 or 6 8. 3 and 7 9. CROSSOVER PROCEDURE.sh. 10. DOUBLE-BLIND PROCEDURE.sh. 11. SINGLE-BLIND PROCEDURE.sh. 12. (crossover* or cross over*).ti,ab. 13. placebo*.ti,ab. 14. (doubl* adj blind*).ti,ab. 15. allocat*.ti,ab. 16. trial.ti. 17. RANDOMIZED CONTROLLED TRIAL.sh. 18. random*.ti,ab. 19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 20. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.) 21. 19 not 20 22. 8 and 21

Science Citation Index search strategy	Topic=((“colorectal neoplasm”) or (“colorectal tumour”) or (“colorectal adenocarcinoma”) or (“colorectal cancer”) or (“colorectal carcinoma”) or (“rectal tumour”) or (“rectal tumour”) or (“rectal cancer”) or (“rectal carcinoma”) or (“rectal neoplasm”) or (“rectal adenocarcinoma”) or (“rectal malignancy”) or (“colorectal malignancy”)) AND Topic=(early) AND Topic=((“local treatment“) or (“local management“) or (“local surgery“) or (“transanal surgery“) or (“local excision“) or (TEM) or (TEMS) or (“transanal endoscopic microsurgery“) or (“endoscopic surgery“) or (“microsurgery“) or (“abdominoperineal resection“) or (“anterior resection“) or ("Hartmann") or ("transanal total mesorectal excision") or (TaTME) or ("transanal minimally invasive surgery") or (TAMIS) or (“transanal endoscopic operation“) or (TEO) or (“transanal single port microsurgery“) or (TSPM)) Refined by: Document Type=(ARTICLE OR PROCEEDINGS PAPER) Databases=SCI-EXPANDED
ClinicalTrials.gov by United States National Library of Medicine (http://www.clinicaltrials.gov)	Condition: rectal cancer. Intervention: (radical OR total OR mesorectal) AND (local OR endoscopic OR transanal OR natural orifice) AND (surgery OR resection OR excision OR microsurgery). Limits: Study type: interventional studies.
International Standard Randomized Controlled Trial	Radical OR local OR transanal OR excision OR TEM OR TAMIS OR TEO OR TSPM

Number Registry (http://www.ISRCTN.com)	
The International Clinical Trials Registry Platform by World Health Organization (http://apps.who.int/trialsearch)	Radical OR local OR transanal OR excision OR TEM OR TAMIS OR TEO OR TSPM.
National Cancer Institute (NCI) Clinical Trials Registry (www.cancer.gov/clinicaltrials)	Cancer Type/Condition: Rectal cancer. Stage/Subtype: stage-I rectal cancer. Trial Type: Treatment. Trial Status: Active.

Appendix B - Criteria for judging risk of bias in the "Risk of bias" assessment tool

RANDOM SEQUENCE GENERATION Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: · Referring to a random number table; · Using a computer random number generator; · Coin tossing; · Shuffling cards or envelopes; · Throwing dice; · Drawing of lots; · Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: · Sequence generated by odd or even date of birth; · Sequence generated by some rule based on date (or day) of admission; · Sequence generated by some rule based on hospital or clinic record number. · Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually

	involve judgement or some method of non-random categorization of participants, for example: · Allocation by judgement of the clinician; · Allocation by preference of the participant; · Allocation based on the results of a laboratory test or a series of tests; · Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: · Central allocation (including telephone, web-based and pharmacy-controlled randomization); · Sequentially numbered drug containers of identical appearance; · Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: · Using an open random allocation schedule (e.g. a list of random numbers);

	· Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); · Alternation or rotation; · Date of birth; · Case record number; · Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: · No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; · Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: · No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;

	· Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: · Insufficient information to permit judgement of 'Low risk' or 'High risk'; · The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: · No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; · Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: · No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; · Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: · Insufficient information to permit judgement of 'Low risk' or 'High risk'; · The study did not address this outcome.

INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: · No missing outcome data; · Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); · Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; · For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; · For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; · Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: · Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; · For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;

	· For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; · 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; · Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: · Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); · The study did not address this outcome.
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	
Criteria for a judgement of 'Low risk' of bias.	Any of the following: · The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; · The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: · Not all of the study's pre-specified primary outcomes have been reported; · One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified;

	· One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); · One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; · The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS Bias due to problems not covered elsewhere in the table.	
Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: · Had a potential source of bias related to the specific study design used; or · Has been claimed to have been fraudulent; or · Had some other problem.
Criteria for the judgement of	There may be a risk of bias, but there is either: · Insufficient information to assess whether an important risk of bias exists; or

'Unclear risk' of bias.	· Insufficient rationale or evidence that an identified problem will introduce bias.

Appendix C - Raw reported data for each oncologic outcome from each study

Outcome	Study	Local excision			Radical resection			Relative effect estimate and test for difference
		Events	Total	Reported estimate	Events	Total	Reported estimate	
Disease-free survival	Winde 1997	1	25	*not reported*	1	28	*not reported*	*not reported*
	Lezoche 2012	6	50	Disease-free survival probability: 88% (95% CI 75 to 94%)	5	50	Disease-free survival probability: 90% (95% CI 78 to 96%)	Log rank test P = 0·686
	Chen 2013	2	28	*not reported*	0	30	*not reported*	*not reported*
Cancer-related survival	Winde 1997	1	25	Survival probability at 5 years: 96% (SD = 4.08)	1	28	5-year survival: 96% (SD = 3.2)	Hazard ratio 1.02 (increased risk with LE) log-rank test x2= 0.0002, P = 0.98
	Lezoche 2012	4	50	survival probability at median 9.6 years: 89% (95% CI 70 to 96)	3	50	survival probability at median 9.6 years: 94% (95% CI 82 to 98)	Log rank test P = 0·687
	Chen 2013	0	28	100%	0	30	100%	P = 1.00
Local recurrence-free survival	Winde 1997	1	25	Local recurrence rate: 4%	0	28	*not reported*	*not reported*
	Lezoche 2012	4	50	Local recurrence rate: 8%	3	50	Local recurrence rate: 6%	Log rank test P = 0·687
	Chen 2013	2	28	Local recurrence rate: 7.1%	0	30	Local recurrence rate: 0%	P = 0.229
Metastasis-free survival	Winde 1997	0	25	*not reported*	1	28	*not reported*	*not reported*
	Lezoche 2012	2	50	Distant metastasis rate: 4%	2	50	Distant metastasis rate: 4%	*not reported*
	Chen 2013	0	28	Distant metastasis rate: 0%	0	30	Distant metastasis rate: 0%	P = 1.00