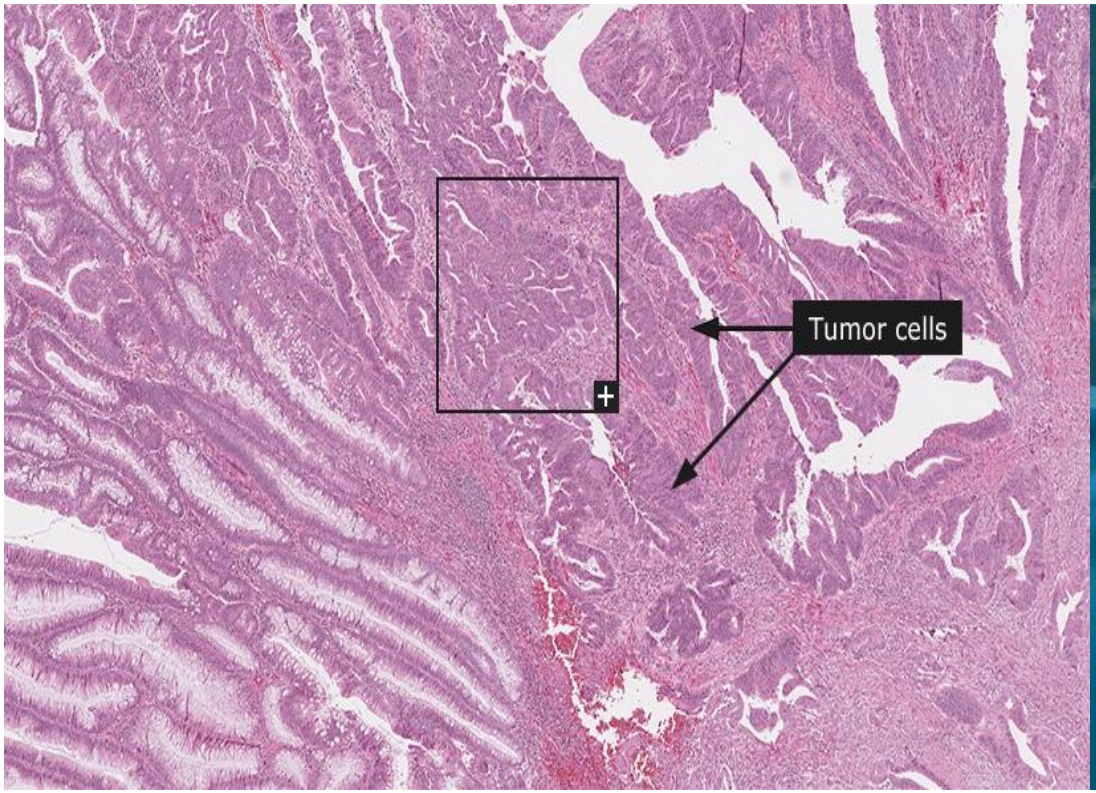
KCE REPORT 260

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART 3: LOCAL VS RADICAL RESECTION FOR STAGE 1 TUMOURS



KCE REPORT 260
GOOD CLINICAL PRACTICE

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GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART 3: LOCAL VS RADICAL RESECTION FOR STAGE 1 TUMOURS

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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ABBREVIATIONS

ABBREVIATION	DEFINITION
AHRQ	Agency for Healthcare Research and Quality
AR	Abdominal resection
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
ELRR	Endoluminal locoregional resection
EMVI	Extramural venous invasion
ERUS	Endorectal ultrasound
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
FU	Fluorouracil
GDG	Guideline Development Group
GIN	Guidelines International Network
HR	Hazard ratios
IKNL	Integraal Kankercentrum Nederland
KCE	Belgian Health Care Knowledge Centre
LR	Local recurrence
LRFS	Local recurrence free survival
LTME	Laparoscopic total mesorectal excision
MA	Meta-analysis
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

NICE	National Institute for Health and Care Excellence
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance
OR	Odds ratio
OS	Overall survival
PET-CT	Positron emission tomography - computed tomography
PICO	Population-intervention-comparator-outcome
PROCARE	Project on Cancer of the Rectum
QoL	Quality of life
RCT	Randomised controlled trial
RQ	Research question
RR	Risk ratio
SEER	Surveillance, Epidemiology and End Results
SR	Systematic review
TAE	Transanal excision
TEM(S)	Transanal endoscopic microsurgery
TME	Total mesorectal excision

SCIENTIFIC REPORT

CAN LOCAL RESECTION OR TRANSANAL ENDOSCOPIC MICROSURGICAL RESECTION BE PERFORMED INSTEAD OF RADICAL RESECTION WITHOUT COMPROMISING THE OUTCOME IN RECTAL CANCER PATIENTS (T1, T2)?

1 INTRODUCTION

Stage I rectal cancer tumours extend either into the submucosa (T1) or into, but not beyond, the muscularis propria (T2), without any evidence of spread into the lymph nodes (N0) nor metastases (M0). Radical resection, which includes the mesorectum and thereby resects lymphatic spread, is considered curative since a five year cancer specific survival of >95% can be expected.[1] For classification we adhere to the TNM Classification of Tumours by the International Union Against Cancer 7th edition: RECTUM (C20), to be found in the Appendix. Stage I involves exclusively T1 and T2, N0. The sm classification by Kikuchi et al. (Kikuchi 1995 Dis Colon & Rectum) describes the depth of invasion into the submosa: in sm1a less than a quarter of the width of the tumour invades the submucosa, in sma 1b a quarter to half of the width of the tumour invades the submucosa, in sma 1c more than half of the width of the tumour invades the submucosa, in sma 3 the tumour invades the submucosa and is close to the muscularis propriae, sm 2 is a stage between sm 1 and sm 3. The sm classification (and others) are used for risk stratification.

The subject is controversial but recent guidelines do not recommend local resection, transanal excision (TAE) or transanal endoscopic microsurgical resection (TEMS) instead of a radical resection for patients with Stage I rectal cancer. The scope is not to compare techniques for local resection. It may be noted that TEMS is considered superior to TAE in some reports. A recent SR by Clancy et al. showed that TEMS had a higher rate of negative microscopic margins in comparison with TAE (OR, 5.281; 95% CI, 3.201-8.712; $p < 0.001$). TEMS also had a reduced rate of specimen fragmentation

(OR, 0.096; 95% CI, 0.044-0.209; p < 0.001) and lesion recurrence (OR, 0.248; 95% CI, 0.154-0.401; p < 0.001) compared with local excision.[2]

The 2015 NCCN guideline on rectal cancer discusses TEMS for stage cT1N0 only, as defined by endorectal ultrasound or MRI and conditional on specific criteria .[3] Inclusion criteria based on the work by Nash et al. [4] specify that the T1 lesion should be limited to less than 30% of the bowel circumference, be less than 3 cm in size with clear margins (>3 mm), be mobile and within 8 cm of the anal verge. The lesion may be identified following endoscopic polyp removal. Lymphovascular and perineural invasion should be excluded and there should be no evidence of lymphadenopathy on pre-treatment imaging.

The 2014 NICE guideline[1] states that there is very little good-quality evidence comparing treatment options for stage I rectal cancer. Since the colorectal cancer screening program was installed in the United Kingdom, an increasing number of stage I rectal cancers is being detected but optimum management remains unclear. Malignant polyps are mostly stage I and are often removed endoscopically. Since the mesorectum remains untouched there is a risk of local recurrence or metastatic spread, particularly to local lymph nodes.

In current practice, the indications for local resection is based on risk stratification. A SR by Bosch et al. on pT1 colorectal cancer analysed risk factors for lymph node metastasis. The strongest independent predictors were lymphatic invasion (RR 5.2, 95 % CI 4.0 - 6.8), submucosal invasion ≥ 1 mm (RR 5.2, 95 %CI 1.8 - 15.4), budding (RR 5.1, 95 %CI 3.6 - 7.3) and poor histological differentiation (RR 4.8, 95 %CI 3.3 - 6.9).[5] This was confirmed in another series reporting risk factors for lymph node metastasis in pT1 (colo)rectal cancer: poor differentiation, tumour budding, lymphovascular invasion and depth of submucosal invasion.[6] The overall risk for nodal involvement in pT1 rectal cancer is about 15%[7] and was observed in 3% of pT1sm1, 8% of pT1sm2 and 23% of pT1sm3 lesions.[8]

Obviously, local resection of any type carries an inherent oncologic compromise as nodes are not removed. It is therefore unclear whether more invasive radical resection should be advised in those cases.To address this uncertainty we undertook a SR of the clinical studies to answer the question whether local resection (any type, TAE or TEMS) can be performed instead of a radical resection without compromising the outcome in patients with stage I (T1, T2) rectal cancer. All types of local surgery were considered, but only in comparison with radical surgery. Critical outcomes were disease free survival (DFS), metastasis free survival (MFS), local recurrence free survival (LRFS), overall survival (OS) and quality of life (QoL).

2 LITERATURE SEARCH AND STUDY SELECTION

SRs and meta-analyses (MA) were searched in the following databases: OVID Medline and PreMedline, EMBASE, Cochrane Database of Systematic Reviews. RCTs and other primary studies were searched in OVID Medline and PreMedline and Pubmed. Hand searching was performed based on reference lists of retrieved manuscripts. The search strategy for Medline can be found in the Appendix. A filter was applied for SRs or for all other types of studies respectively.

All citations retrieved from the systematic literature search were screened based on title and abstract. Relevant citations were further evaluated based on the full text. Selection criteria are described in the Appendix.

The search for SRs and meta-analyses published up until March 2015 retrieved 2214 citations after removal of duplicates. The further selection process, (summarized in the Appendix), yielded 50 SRs and/or meta-analyses for full text analysis. Five studies were selected[2, 9-12] but three were comparisons between two types of local surgical interventions[2, 11, 12] and were further excluded. Finally two MA were retained for data extraction: one evaluated local excision without any other therapeutic intervention[9] the second evaluated local excision after neoadjuvant chemoradiotherapy.[10] Both MA included one (different) RCT and otherwise only observational studies.[13, 14]

The search for primary studies between January 1, 2013 (last search dates of the selected SR were September and July 2013) and March 26, 2015 yielded 1 360 citations, from which 28 duplicates were eliminated. The selection based on title and abstract yielded 14 references for full text analysis. Of these only one RCT[15] fitted the inclusion criteria. Thus, this selection process yielded 3 RCTs for data extraction (see Appendix).

3 CRITICAL APPRAISAL OF THE SELECTED LITERATURE

The SRs were appraised using the AMSTAR checklist (http://amstar.ca) (see Appendix). Both MA pooled results from observational studies with one RCT. Pooling non-randomised studies is problematic because of heterogeneity[16] therefore the score for appropriateness of the methods to combine study findings was not attributed.

The newly identified RCT was appraised using the Cochrane Risk of Bias tool [16] as shown in the Appendix. For the two RCTs included in the published MA, the reported quality appraisal was adopted.

4 DATA EXTRACTION AND STATISTICAL ANALYSIS

Data extraction was summarized for the SRs and for the primary studies (see Appendix). The selected SRs pooled data obtained from one RCT and 12 observational studies [9] and one RCT and seven observational studies.[10] The subgroup analysis for stage T3 was considered out of scope. The Cochrane Handbook recommends not to use such methodology.[16] We therefore reported the outcomes of the primary studies as ranges. However, the three RCTs were pooled using Review Manager Version 5 (The Cochrane Collaboration, Updated February 2011).

5 EVIDENCE DESCRIPTION

5.1 Systematic reviews

5.1.1 Overall survival

Kidane et al.[9] reported unadjusted risk ratios (RR) for 5 year OS from 12 observational studies ranging from 0.11 to 2.87. Seven studies compared TAE to radical resection (RR 0.94 to 2.87) and five studies compared TEMS to radical resection (RR 0.11 to 1.53). The authors stated that results were not influenced by a higher proportion of tumours located in the lower third of the rectum because meta-regression in case of similar ratio of lower-third cancers was not significant.[9] Shaikh et al.[10] reported odds ratios (OR) ranging from 0.25 to 5.34 for 10 year OS from four studies comparing local resection to radical resection and including all disease stages. Again, these OR were unadjusted. Given the wide ranges no conclusion can be reached regarding OS based on these observational studies.

5.1.2 Disease free survival

Five year DFS reported by Kidane et al.[9] using unadjusted risk ratios from ten observational studies comparing local resection to radical resection ranged from 0.31 to 8.31. For patients who received TAE (five studies) the RR ranged from 0.31 to 2.17 and for those who received TEMS (five studies) the RR ranged from 0.49 to 8.31. The highest value in favour of radical resection is reported in a subgroup of high risk patients by Heintz et al.[17] The 5 year DFS reported by Shaikh et al.[10] based on five studies across all stages is expressed by OR ranging from 0.26 to 5.34.

5.1.3 Local recurrence

Local recurrence after five years was more frequent after local resection in all of the 13 reported observational studies included by Kidane et al.[9] The unadjusted RR ranged from 1.48 to 36.56, in favour of radical resection, for the entire group. In the eight studies comparing transanal resection to radical resection the RR ranged from 1.89 to 11.7. In the five studies comparing TEMS to radical resection the RR ranged from 1.48 to 36.56. Shaikh et al.[10] reported OR for local recurrence from seven studies including various cancer stages and with variable follow-up and ranging from 0.26 to 2.19.

5.1.4 Postoperative complications, stoma and perioperative mortality

Since quality of life (QoL) was not reported, we describe other related secondary outcomes. The review by Kidane[9] reported on seven studies with lower rates of major postoperative complications after local resection. The unadjusted RR ranged from 0.06 to 0.92 for the entire group. These low and high values originate from the group of patients undergoing TEMS (5 studies). In the group receiving transanal excision (2 studies) the RR ranged from 0.22 to 0.47. The type of major postoperative complications that were included was not further specified.

The RR for permanent stomas ranged from 0.02 to 2.08 in six studies comparing TAE with radical resection and from 0.03 to 0.5 in five studies comparing TEMS with radical resection.[9]

Perioperative mortality was reported in two observational studies on TAE and radical resection included in the review by Kidane et al.[9]. The RR were 0.28 and 1.22. In three other observational studies comparing TEMS with radical resection, the RR ranged from 0.13 to 0.17.

5.2 Primary studies

Three selected RCTs addressed the RQ adequately. Patients with local rectal cancer were randomly assigned to TEMS (n=28) or laparoscopic lower anterior resection (n=30).[15] In a second study patients staged T2N0M0 with repeat staging after adjuvant chemotherapy were randomly assigned to TEMS or laparoscopic total mesorectal excision (TME) (50 patients in each group).[14] In the third study patients were randomly assigned to TEMS (n=24) or AR (n= 26).[13]

5.2.1 *Overall survival*

Only Chen et al.[15] reported OS which was 100% for both groups after one year.

5.2.2 *Local recurrence and distal metastasis*

The outcomes for local recurrence (LR) and distant metastasis from the three RCTs were pooled (Figure 1)

,Figure 2). Local recurrence was more frequent after local resection (RR 1.90, 95% CI: 0.57-6.32) but significance was not reached because of the low event rate (p=0.30). The occurrence of distal metastasis was not different (RR 0.76, 95% CI: 0.15-3.91).

Figure 1 – Forest plot for local recurrence after local resection (TEMS) vs abdominal resection

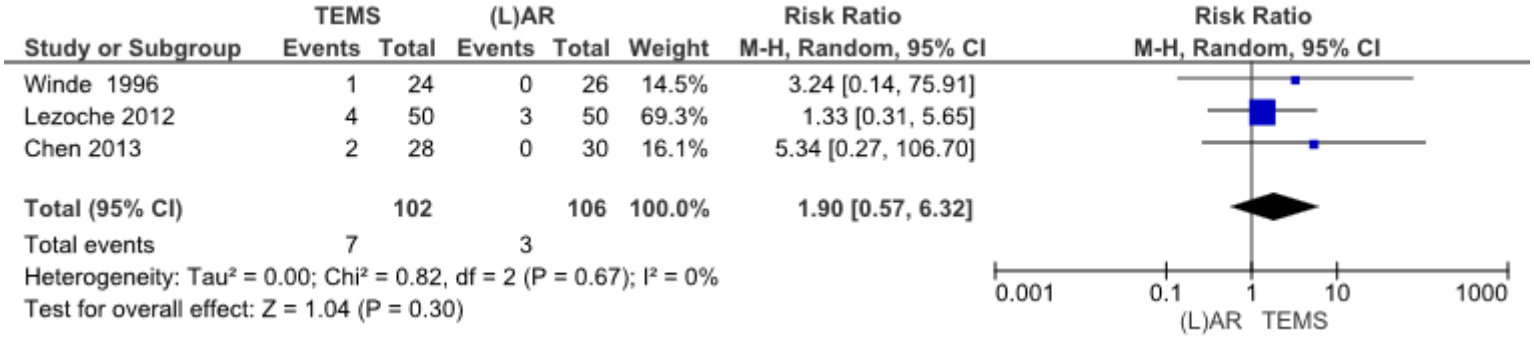
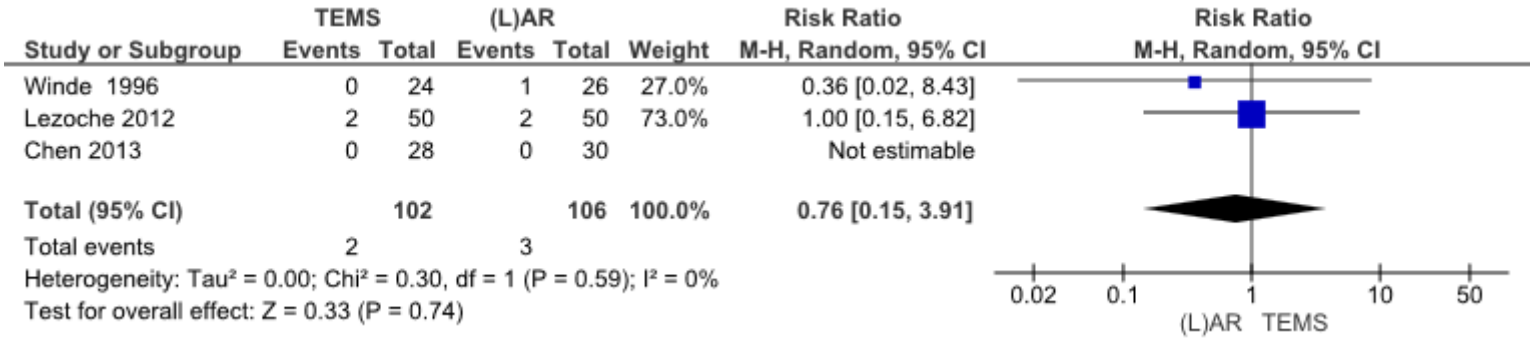


Figure 2 – Forest plot for distant metastasis after local resection (TEMS) vs abdominal resection



5.2.3 Secondary outcomes

QoL was not reported. Other outcomes representing QoL were considered when they were reported in at least two publications. These secondary outcomes were: blood loss and operative time (reported in 3/3) and conversion rate, blood transfusion and hospital stay (reported in 2/3). Because these data were mostly not reported as means ± SD they could not be pooled. We therefore report the ranges in Table 1. Blood loss was higher, more than double with open, abdominal surgery and operative time was longer in all three RCTs. Conversion to another type of surgery occurred only in TEMS group in 2/30 patients.[15] The need of blood transfusion was reported by Chen et al.[15] and Lezoche et al.[14] The TEMS group never required transfusion as opposed to the abdominal resection group that did in a few cases.

Hospital stay, reported by Winde et al. and Lezoche et al.[13, 14] was more than twice as long following abdominal resection.

Table 1 – Secondary outcomes from primary studies

Study	TEMS	(L)AR	Units
1. Blood loss (ml)			
Chen et al.[15]	40.7 (±13.6)	93.7 (±39.5)	mean±SD
Lezoche et al.[14]	45.0 (45-45)	200.0 (100-350)	median+IQ range
Winde et al.[13]	143.0 (±55)	745.0 (±70)	mean±SD
2. Operative time (min)			
Chen et al.[15]	130 (±16.7)	198 (±16.8)	mean±SD
Lezoche et al.[14]	90 (90-100)	174 (160-190)	median+IQ range
Winde et al.[13]	103	149	average
3. Conversion rate			
Chen et al.[15]	2/30	0/30	number
Lezoche et al.[14]	0 (0)	5 (10)	number (percentage)
4. Blood transfusion			
Chen et al.[15]	0/30	1/30	number
Lezoche et al.[14]	0 (0)	10 (20)	number (percentage)
5. Hospital stay (days)			
Lezoche et al.[14]	3.0 (3-4)	6 (5-7)	median + IQ range
Winde et al.[13]	5.7 (±1.8)	15 (4±1.5)	mean±SD

5.3 Grading outcomes

The evidence was graded only for the pooled outcomes from the RCTs.[13-15] Grade profiles [18] are illustrated in Table 2. Strength of recommendation was assigned by the GDG.

Table 2 – Grade profiles

Local resection for T 1-2 rectal cancer

Patient or population: T 1-2 rectal cancer
Settings:
Intervention: Local resection

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Local resection	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence Comments (GRADE)
Local recurrence Follow-up: mean 54 months	**28 per 1000**	**54 per 1000** (16 to 179)	**RR 1.9** (0.57 to 6.32)	208 (3 studies)	⊕⊖⊖⊖ **very low**[1,2]
distant metastasis Follow-up: mean 54 months	**28 per 1000**	**22 per 1000** (4 to 111)	**RR 0.76** (0.15 to 3.91)	208 (3 studies)	⊕⊖⊖⊖ **very low**[1,2]
blood loss	Not estimable	The median blood loss in the intervention group ranged from 53 to 602 lower		208 (3 studies)	⊕⊕⊖⊖ **low**[1,3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] no allocation concealment
[2] confidence interval includes both serious harm and serious benefit
[3] effect ranges from 53 to 602

6 CONCLUSIONS AND RECOMMENDATIONS

The conclusions are formulated regarding stage I rectal cancer (T1, T2, N0) as a whole.

Conclusions

- There is no evidence from RCTs on the superiority of local vs. radical resection for OS and based on observational studies no conclusion can be reached.
- There is no evidence from RCTs on the superiority of local vs. radical resection for DFS and based on observational studies no conclusion can be reached.
- The evidence on LR is of very low quality and allows no conclusion since the 95% CI include both harms and benefits.
- The evidence on distant metastases is of very low quality and allows no conclusion since the 95% CI include both harms and benefits.
- Blood loss is more important during radical surgery (low quality evidence).
- RCTs show a tendency for longer operative time, longer hospital stay and more blood transfusions with radical surgery.
- Observational studies suggest that major postoperative complications are less frequent following local resection.
- Observational studies report a lower number of permanent stomas and perioperative deaths following local resection.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is no good evidence that local resection does not harm by leading to increased local recurrence or metastases. Benefits of the intervention (local resection) are less blood loss, a lower number of permanent stoma and shorter hospital stay. Local resection may be perceived as leading to less complications but its safety is not established. A registry compiling clinical data and follow-up of patients treated with local resection is advisable.
Quality of evidence	The evidence is based on only three RCTs. Two SR of observational studies have pooled not adjusted RR or ORs and are therefore methodologically flawed. A recent guideline from the European Society of Gastrointestinal Endoscopy (ESGE) states "that the majority of (colonic and) rectal superficial lesions can be effectively removed in a curative way by standard polypectomy and/or by endoscopic mucosal resection. Endoscopic submucosal resection can be considered for removal of (colonic and) rectal lesions with high suspicion of limited colonic invasion based on two main criteria of depressed morphology and irregular or nongranular surface pattern, particularly if the lesions are larger than 20 mm."
Costs (resource allocation)	Cost is out of scope for this report.
Patients values and preferences	Regarding patient preferences on local vs. radical excision for low T1/T2 rectal cancers one study by Solomon et al. was identified [19]. Hundred patients were studied using time trade off/standard gambles method. The information presented was that local excision may lead to reduced survival but will avoid permanent stoma. Most patients were prepared to gamble reduced survival to avoid stoma.

Recommendations	LoE	Strength of recommendation
Radical resection should be used in patients with T2 rectal cancer.	Very low	Strong
'En bloc' complete local resection is considered sufficient when pathology report and staging confirms pT1 sm1. Discussion by a multidisciplinary team and adequate surveillance is mandatory.	Expert consensus	Strong
pT1 sm2 sm3 should be discussed by a multidisciplinary team, if no contraindication radical surgery is recommended.	Expert consensus	Strong

APPENDIX

Figure 3 – Flow chart for selection of SR

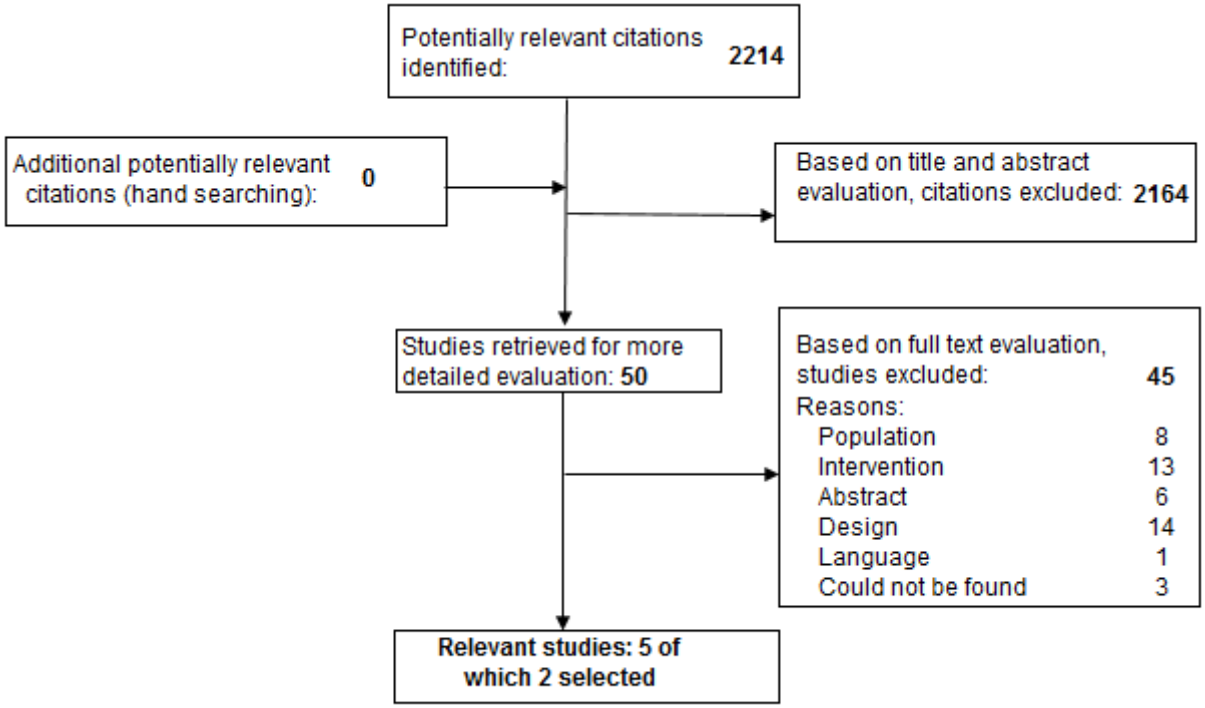


Figure 4 – Selection primary studies

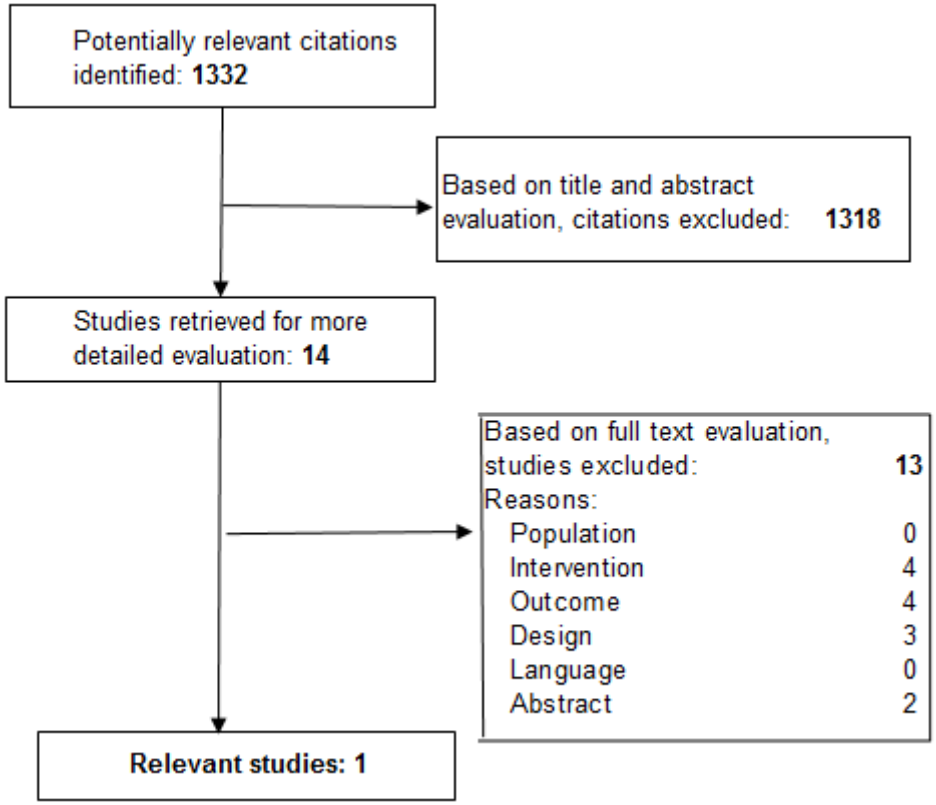


Table 3 – Search strategy

Date	March 2015
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy	1 exp Colorectal Neoplasms/ (152497) 2 ((rectum or rectal or colorectal) adj4 (cancer* or tumour* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti. (103863) 3 1 or 2 (176686) 4 resect*.ab,ti. (250476) 5 ablat*.ab,ti. (73386) 6 laparoscop*.ab,ti. (87063) 7 exp laparoscopy/ (71249) 8 debulk*.ab,ti. (4980) 9 cryosurg*.ab,ti. (3722) 10 cryoablat*.ab,ti. (2267) 11 radioablat*.ab,ti. (122) 12 thermoablat*.ab,ti. (280) 13 radiofrequency-ablat*.ab,ti. (9430) 14 su.xs. (1666764) 15 surger*.ab,ti. (807385) 16 surgical.ab,ti. (694708) 17 proctectom*.ab,ti. (896) 18 excis*.ab,ti. (135312) 19 exp Microsurgery/ (27103) 20 microsurg*.ab,ti. (19420) 21 dissect*.ab,ti. (124799) 22 hybrid techniqu*.ab,ti. (768) 23 TLE.ab,ti. (2796) 24 TAE.ab,ti. (1606) 25 (TEM or TEMS).ab,ti. (26648) 26 ESR.ab,ti. (14196) 27 ESD.ab,ti. (2304)

	28 APR.ab,ti. (2516) 29 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (2568833) 30 3 and 29 (58565) 31 limit 30 to systematic reviews (1398) 32 limit 31 to yr="2006 -Current" (1070)

Table 4 – Selection criteria for all types of studies

Review question	**Can a local resection or transanal endoscopic microsurgical resection be performed instead of a radical resection without compromising the outcome in rectal cancer patients**	
Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with stage I (T1-T2) rectal cancer , also after adjuvant therapy	all other stages of rectal cancer
Intervention	local resection, TEMS and as comparator radical surgery open or laparoscopic	any other intervention or comparator or absence of intervention
Outcome	PFS, MFS, LRFS, OS, QoL	cost
Design	SR, meta-analysis, RCT, observational studies	case reports, abstracts, reports with available update
Language	English, French, German, Dutch, Spanish	other languages
Availability	full text available	no full text available

Table 5 – Amstar checklist for SR

Reference	"a priori" design provided?	Duplicate study selection?	Comprehensive literature search?	Status of publication used as inclusion criteria?	List of included and excluded studies provided?	Characteristics of included studies provided?	Scientific quality of included studies assessed and documented?	Scientific quality of included studies appropriately used to formulate conclusions?	Appropriate methods used to combine study finding?	Publication bias assessed?	Conflicts of interests reported?	Total score
Kidane 2015	YES	YES	YES	YES	NO	YES	YES	YES	NO	YES	NO	9/11
Shaikh 2015[20]	YES	YES	YES	YES	NO	YES	YES	YES	NO	YES	NO	8/11

Table 6 – Cochrane Risk of Bias tool

Reference	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Chen 2013	Low risk	Unclear risk (not reported)	High risk (not feasible)	Low risk	Low risk	High risk (differences in adjuvant therapy)

Table 7 – Evidence table of the systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Kidane 2015	• SR and MA • Funding: none • Search date: September 27,2013 • Databases: Medline, Embase, Central, Cinahl,www.clincaltrials.gov, ISI Web of Science, conference proceedings • Study designs: RCT, observational studies: retrospective and prospective cohort • N included studies: N=13 (1 RCT: 53 patients, 12 observational studies: 2802 patients) (Winde,1996;Heintz,1998;Ambacher,1999;Mellgren,2000;Lee,2003;Nascimbeni,2004;Endresth,2005;Ptok,2007;You,2007;Tarantino,2008;De Graaf,2009;Nash,2009;Palma,2009)	• Eligibility criteria: ○ Patients with rectal cancer T1N0M0 treated with radical resection or local resection including TAE, TEMS and TAMIS. • Patients > 18 yrs	Radical resection vs local resection including TAE, TEMS and TAMIS.	5 yr OS: local resection in comparison with radical resection RR 1.46; 95% CI 1.19–1.77, p = 0.0002 but 1) no difference in 5-year OS for TEMS vs radical resection 2) meta-regression in case of similar ratio of lower-third cancers: (RR, 1.13; 95% CI, 0.93–1.37) ns • All postoperative complications: lower with local resection: pooled RR 0.16 ;95% CI, 0.08–0.30; • Major postoperative complications: lower with local resection: pooled RR 0.20;95% CI, 0.10–0.41;*p <0.00001* • Stoma (QOL): lower with local resection RR, 0.17; 95% CI, 0.09–0.30, p < 0.001	• 5 yr DFS: RR 1.54; 95% CI 1.15-2.05; *p=0,003* • 5 yr DSS: RR 2.00; 95% CI 1.29-3.09; *p=0,002* • 5yr LR: increased with local resection: RR 2.36; 95% CI, 1.64–3.39, p < 0.00001 • Perioperative mortality lower with local resection: RR, 0.31;95% CI, 0.14–0.71, p = 0.005	• Amstar 9/11 items score 'yes' • Pooled observational studies: controversial methodology

Shaikh 2015	• SR and MA • Funding: none • Search date: 1946 to July ,2013 • Databases: Medline, Pubmed/Ovid databases and Google Scholar. • Study designs: RCT, observational studies: retrospective and prospective cohort • N included studies: N=8 (1 RCT: 100 patients, 7 observational studies: 1301 patients) • (Bannon,1995; Bonnen, 2004; Callender, 2010; Caricato, 2006; Habr-Gama, 1998; Huh, 2008; Kunderl, 2010; Lezoche, 2012)	• Eligibility criteria • Patients with rectal adenocarcinoma, any stage and post neoadjuvant chemoradiotherapy	radical resection (RS) vs local resection (LE) including only studies with direct comparison	10 yr OS (pooled 4 studies): LE in comparison with RS : OR 0.96 ; 95% CI 0.38-2.43, *p* = 0.93 10 yr OS RCT no significant difference LR (pooled 7 studies): 16/157, 10,1% in LE group vs 95/1144,8% in RS group: OR 1.29, 95% CI 0.72-2,31, p=0.40; LR in RCT: 8% in LE 6 % in RS group 5 yr DFS (pooled 5 studies) OR 1.04, 95% CI 0.61-1.76,P=0.89 DFS in RCT: no significant difference	• Differences on pre-treatment stage – subgroup analyses for T3: out of scope	• Amstar 9/11 items score 'yes' • Pooled observational studies: controversial methodology

Table 8 – Evidence table primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal
Chen 2013	RCT: open but random assignment of treatment	Eligibility criteria: • rectal cancer staged T1-2N0M0 • according to NCCN guidelines, tumour location 6-15 cm proximal to the anal verge, moderately to highly differentiated adenocarcinoma, acceptable physical tolerance Exclusion criteria: Previous surgery n=60 FU: 5yrs	Transanal endoscopic microsurgery (TEMS) (n=28) vs laparoscopic lower anterior resection (LAR) (n=30)	1 yr OS 100% in both groups Local recurrence 7.1% for TEMS vs 0% for LAR (ns) Distant metastases: o in both groups Adjuvant Chemotherapy: 3.6% (TEMS) vs 26.7% (LAR) p=0.026 Operative time: 130±.16.7 min vs 198.7±16.8 min p<0.001 Blood loss: 40.7± 13.6 ml vs 93.7±39.5 ml p<0.001 Conversion rate, en bloc resection rate, major intraoperative events, blood transfusions: no differences	Pathological outcomes: Clean margins, histological staging and pathological types: no differences	High risk for allocation concealment and differences in adjuvant therapy
Lezoche 2012	RCT: open but random	Eligibility criteria: rectal cancer staged T2N0M0	Endoluminal locoregional resection (ELRR) performed by	Local recurrence or distant metastases (5 yr FU): 4+2 in ELRR group	A significant difference was found for the following secondary outcomes-	

(included in SR by Saikh 2015)	assignment of treatment	according to NCCN guidelines, repeat staging after adjuvant chemotherapy, fitness *grade I-II* according to American Society of Anaesthesiologists tumour location within 6 cm of the anal verge, moderately (G2) to well (G1) differentiated adenocarcinoma, tumour diameter ≤3cm Exclusion criteria: Higher risk patients ASA II-IV, tumours located > 6cm from the anal verge, poorly (G3) or undifferentiated (G4) tumours, lymphovascular or perineural invasion n=100 minimal FU: 5 yrs	transanal endoscopic microsurgery (TEM) (n=50) vs laparoscopic total mesorectal excision (TME) (n=50)	and 3+2 in TME group , not significant (p=0.686) cumulative probability of developing recurrence or metastasis at 5 yrs (12 % vs 10% but events occurred earlier in ELRR group leading to RR 14.24 (95%CI 1.36-149) p=0.27. Blood loss also had a significant effect on the primary outcome (RR 1.01 95%CI 1.00- 1.01 p<0.001)	values given are median with (interquartile range) – always ELRR first, compared with TME 1.Intraoperative programme change: 0(0) vs 6 (12) p=0.013 2.conversion to open surgery: 0(0) vs 5(10) p=0.028 3. temporary stoma: 0(0) vs 11(22) p<0.001 4. definitive stoma: 0(0) vs 12(24) p<0.001 5.duration of operation (min): 90(90-100) vs 174(160-190) 6.blood loss (ml) 45(45-45) vs 200 (100-350) p<0.001 7. # patients receiving transfusion: 0(0) vs 10(20) p<0.001 8. # patients receiving analgesia: 7(14) vs 50(100) p<0.001 9. hospital stay (days): 3(3-4) vs 6(5-7) p<0.001 There was no significant difference in 1. minor postoperative complications: 6(12) vs 7 (14) p=0.766 2. major postoperative complications: 1(2) vs 3(6) p=0.25	

Winde 1996 (included in SR by Kindane 2015)	RCT: open but random assignment of treatment	Eligibility criteria: Patients with rectal adenocarcinoma GI//II and uT1N negative (staging with intraluminal ultrasound) – Tumours were located within 18 cm of the anal verge. Group A underwent TEM (n=24) had a mean age of 63.7 yrs (range 36-90 yrs); M/F ratio 0.7 Group B underwent AR (n=26) had a mean age of 60.9 yrs (range 47-81); M/F ratio 1.2 Follow up of a mean of 40.9 mo in TEM group and 45.8 mo in AR group.	TEM n=24 AR=26	Local recurrence: 1/24 in TME group, none in AR group Distant metastases: 1/26 in AR group, none in TME group	1.operation time: average TEM 103 min vs AR 149 min , p<0.05 2. blood loss: TEM 143±55 ml vs AR 745±70 ml, p<0.001 3.hospital stay: TEM 5.7±1.8 days vs AR 15.4±1.5 days, p<0.0001 4. analgesic (opiates) prescription: TEM average of 5.7 mg/d vs AR 15 mg/d, p<0.0001 5. early (≤ 30 days) complications: TEM 5/24 vs AR 9/26 6. late complications: other than local recurrence or distant metastases: TEM 1/24 vs AR 5/26 5. survival: One patient died in each group HR of dying after TEM was 1.02

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