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Systematic review

Meta-analysis of oncological outcomes after local excision of pT1–2 rectal cancer requiring adjuvant (chemo)radiotherapy or completion surgery

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Background: **Completion total mesorectal excision (TME) is advised for high-risk early (pT1/pT2) rectal cancer following transanal removal. The main objective of this meta-analysis was to determine oncological outcomes of adjuvant (chemo)radiotherapy as a rectum-preserving alternative to completion TME.**

Methods: **A literature search using PubMed, Embase and the Cochrane Library was performed in February 2015. Studies had to include at least ten patients with pT1/pT2 adenocarcinomas that were removed transanally and followed by either adjuvant chemoradiotherapy or completion surgery. A weighted average of the logit proportions was determined for the pooled analyses of subgroups according to treatment modality and pT category.**

Results: **In total, 14 studies comprising 405 patients treated with adjuvant (chemo)radiotherapy and seven studies comprising 130 patients treated with completion TME were included. Owing to heterogeneity it was not possible to compare the two strategies directly. However, the weighted average local recurrence rate for locally excised pT1/pT2 rectal cancer treated with adjuvant (chemo)radiotherapy was 14 (95 per cent c.i. 11 to 18) per cent, and 7 (4 to 14) per cent following completion TME. The weighted averages for distance recurrence were 9 (6 to 14) and 9 (5 to 16) per cent respectively. Weighted averages for local recurrence rate after adjuvant chemo(radiotherapy) and completion TME for pT1 were 10 (4 to 21) and 6 (3 to 15) per cent respectively. Corresponding averages for pT2 were 15 (11 to 21) and 10 (4 to 22) per cent respectively.**

Conclusion: **A higher recurrence rate after transanal excision and adjuvant (chemo)radiotherapy must be balanced against the morbidity and mortality associated with mesorectal excision. A reasonable approach is close follow-up and salvage mesorectal surgery as needed.**

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Introduction

Local excision of early rectal carcinoma results in reduced morbidity and better functional outcome than radical surgery[1,2]. A stoma is generally avoided. Only patients with low-risk T1 carcinomas (well to moderately differentiated, no lymphatic or venous invasion, diameter less than 3 cm and a clear resection margin) are considered to have an acceptable oncological outcome after local excision without further treatment[3,4]. If one or more risk factors are present, local recurrence rates of up to 25 per cent have been reported, so completion total mesorectal excision (TME) is recommended by many national treatment guidelines[5–9].

A rectum-preserving regimen with adjuvant (chemo)-radiotherapy after local excision may be a valid alternative to completion TME in intermediate-risk pT1/pT2 rectal cancer. This approach potentially decreases the risk of local and distant recurrence by sterilizing mesorectal lymph nodes and the excision bed, with expected lower morbidity and similar long-term survival[7,10,11]. The aim of this study was to determine oncological outcomes with adjuvant (chemo)radiotherapy as an organ-preserving alternative to completion TME in this setting.

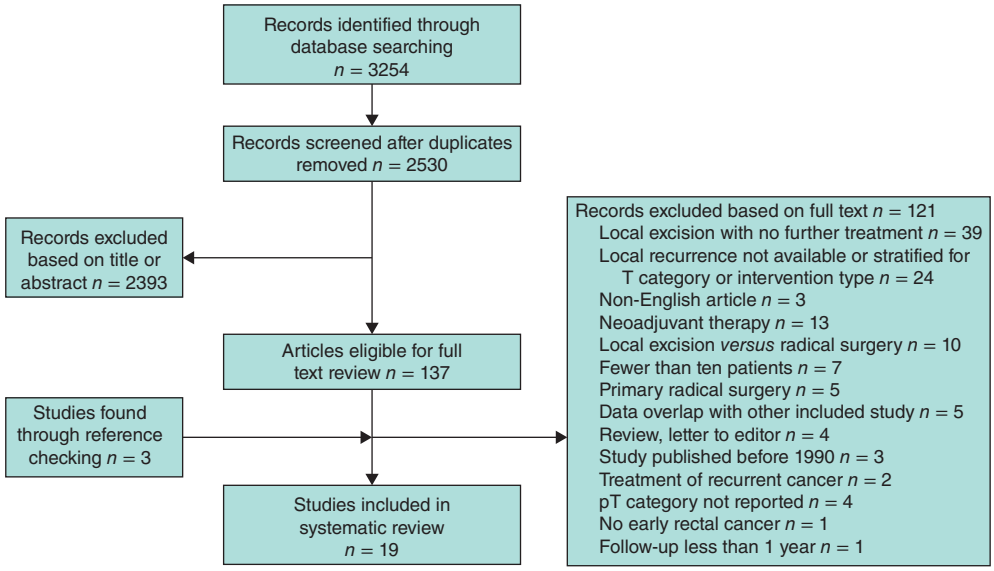


Fig. 1 Flow diagram of literature search

Table 1 Baseline characteristics of studies on local excision and adjuvant (chemo)radiotherapy

Reference	Size of cohort	Intervention‡	T category	Adjuvant therapy†‡	Indication for adjuvant therapy
Sun *et al.*[14]	49	TAE	T1: 8 T2: 41	RT: 15–50 Gy (13) 45 Gy (4) 10–60 Gy (14) 21–67 Gy (21)	n.r.
Ramirez *et al.*[15]	28	TEM	T1: 6 of 30 T2: 24 of 30 (2 were LTFU)	RT: 50·4/28 Gy	pT1 high-risk (G3–4/L1/V1/R0) pT2 low-risk (G1–2 + L0 + V0 + R0)
Morino *et al.*[21]	19	TEM	T2: 19	CHRT: details n.r.	pT2: patients who refused radical surgery
Greenberg *et al.*[16]	51	TAE/trans-sphincteric/transrectal	T2: 51	CHRT: 5-FU + 50·4/28 Gy	All pT2
Duek *et al.*[32]	12	TEM	T2: 12	RT: details n.r.	pT2 with clear resection margins
Min *et al.*[17]	19	LE	T1: 11 T2: 8	RT: 45/25 + 5·4 Gy (7) CHRT: 5-FU + 45/25 + 5·4 Gy (12)	pT1 high-risk (G3–4/L1/V1/R1) All pT2
Gopaul *et al.*[24]	15	LE	T1: 4 T2: 11	RT: 45/25 Gy (10 of 19 patients with T1–T3 disease) CHRT: 5-FU + 45/25 Gy (9 of 19)	pT1–2, based on physician preference
Stipa *et al.*[25]	7	TEM	T1: 3 T2: 4	CHRT: details n.r.	n.r.
Mendenhall *et al.*[23]	67	TAE 65; 2 trans-sacral	T1: 34 T2: 12 T3: 2 No data: 19	RT: 45/25 + 10 Gy (48) *or* 27–50·4/25 + 15 Gy (19)	pT1 high-risk (G3–4/Rx/R1/perineural invasion) All pT2
Lamont *et al.*[18]	20	TAE	T1: 10 T2: 10	CHRT: 5-FU + 45/25 or 46/22 Gy	No strict guideline
Wagman *et al.*[19]	31	TAE 28; proctectomy 9; polypectomy 2	T1: 6 T2: 25	RT: 45/25 + 3·6–10·8 Gy (31) CHRT: 5-FU + RT (16)	pT1 high-risk (G3–4/L1/R1) All pT2
Steele *et al.*[22]	51	TEM	T2: 51	CHRT: 5-FU + 54/30 Gy	All pT2
Taylor *et al.*[20]	21	TAE	T1: 12 T2: 9	RT: 45–50/25 Gy	No strict guideline
Coco *et al.*[31]	15	TAE	T2: 15	RT: 44·6/25 Gy	T2 with clear resection margins

Values in parentheses are *ranges and †number of patients. ‡Values for the total population. TAE, transanal excision; RT, radiotherapy; n.r., not reported; TEM, transanal endoscopic microsurgery; LTFU, lost to follow-up; G3–4, poorly differentiated or undifferentiated; L1, lymphatic invasion; V1, venous invasion; G1–2, well to moderately differentiated; CHRT, chemoradiotherapy; 5-FU, 5-fluoruracil; LE, local excision; R1, non-radical resection; Rx, equivocal radicality.

Table 2 Baseline characteristics of studies on local excision and completion transanal excision

Reference	Size of cohort	Intervention	Interval between TEM and TME*	T category	Indication for completion TME
Morino *et al.*[21]	Total: 107–TP: 5	TEM + TME	n.r.	T2: 5	All pT2
Borschitz *et al.*[27]	Total: 175–TP: 39	TEM + TME	Within 4 weeks	T1: 19 T2: 20	pT1 high-risk (G3–4/L1/V1/R1/Rx/R < 1 mm) and all pT2
Lee *et al.*[26]	Total: 36–TP: 9	TEM + TME	n.r.	T1: 3 T2: 6	pT1 high-risk (G3–4/L1/V1/R1/mucinous carcinoma) and all pT2
Min *et al.*[17]	Total: 76–TP: 7	LE + TME	n.r.	T2: 7	pT1 high-risk (G3–4/L1/V1/R1) and all pT2
Hahnloser *et al.*[28]	Total: 52–TP: 37	TEM + TME	Within 4 weeks	T1: 29 T2: 8	All pT1–2
Nakagoe *et al.*[30]	Total: 11–TP: 11	TEM + TME	Median 35 (7–113) days	T1: 81 T2: 3	pT1 high-risk (G3–4/L1/V1/R0/submucosal invasion > 200–300 μm from muscularis mucosa) and all pT2
Heintz *et al.*[29]	Total: 103–TP: 22	TEM + TME	n.r.	T1: 22	pT1 low-risk (before 1988: G1–2 + L0 + R0–1) and pT1 high-risk (after 1988: G3–4 + L1 + R0–1)

*Values in parentheses are ranges. †Values for the total population; ‡values for target population. TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; n.r., not reported; G3–4, poorly differentiated or undifferentiated; L1, lymphatic invasion; V1, venous invasion; R1, non-radical resection; Rx, equivocal radicality; LE, local excision; G1–2, well to moderately differentiated.

Methods

Search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[12]. MEDLINE (PubMed), Embase (Ovid) and the Cochrane Library were searched systematically. The final search was carried out on 23 February 2015. Details of the search are presented in *Appendix S1* (supporting information).

Included studies had to present data on rectal adenocarcinoma with a pathologically proven T1 or T2 category, treated with local excision followed by either adjuvant (chemo)radiotherapy or completion TME. Studies had to include at least ten patients per clinical T category, with a minimum follow-up of 1 year. Included local resection techniques were transanal endoscopic microsurgery (TEM), transanal excision (TAE), excision using a trans-sphincteric or transrectal approach, and excision through a midline posterior proctotomy. Studies were included independent of resection margin status. Exclusion criteria were neoadjuvant therapy before local excision, metastasis or mesorectal lymphadenopathy on imaging at the time of local excision, and articles published before 1990. Animal studies, reviews, letters to the editor and non-English-language articles were also excluded.

The reference lists of included studies were cross-checked to identify additional studies. When studies described a patient population with early rectal cancer from which only a subgroup met the inclusion criteria, only this subgroup was included in the analysis.

Two reviewers independently assessed all titles, abstracts and full texts for potential inclusion. When required, a third researcher was consulted. Included articles based on full text were checked for overlapping statistical data with other studies.

Quality assessment

For quality assessment, a modified version of the Methodological Index for Non-Randomized Studies (MINORS) checklist[13] was used. In addition to the standard eight questions proposed by the checklist, an extra question was added to assess allocation bias. If the included study had a strict protocol for the assignment of either adjuvant (chemo)radiotherapy or completion TME based on pathology, it received the maximum of 2 points for this question. If there was no protocol and the selection was based on physician preference, the study would score no points.

Outcome measures and statistical analysis

The primary outcome was local recurrence. Secondary outcome measures were distant recurrence, overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS). Survival endpoints (OS, DFS and DSS) were extracted as reported by the included

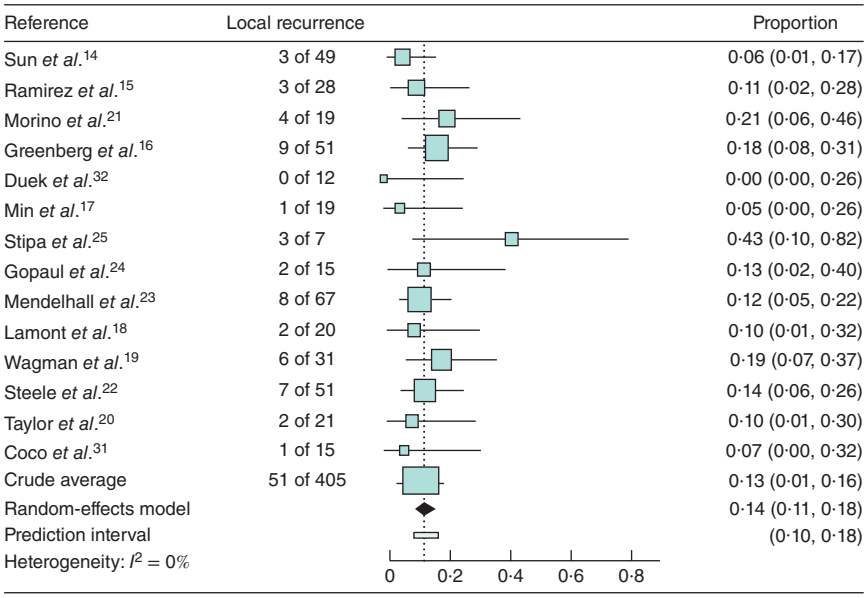
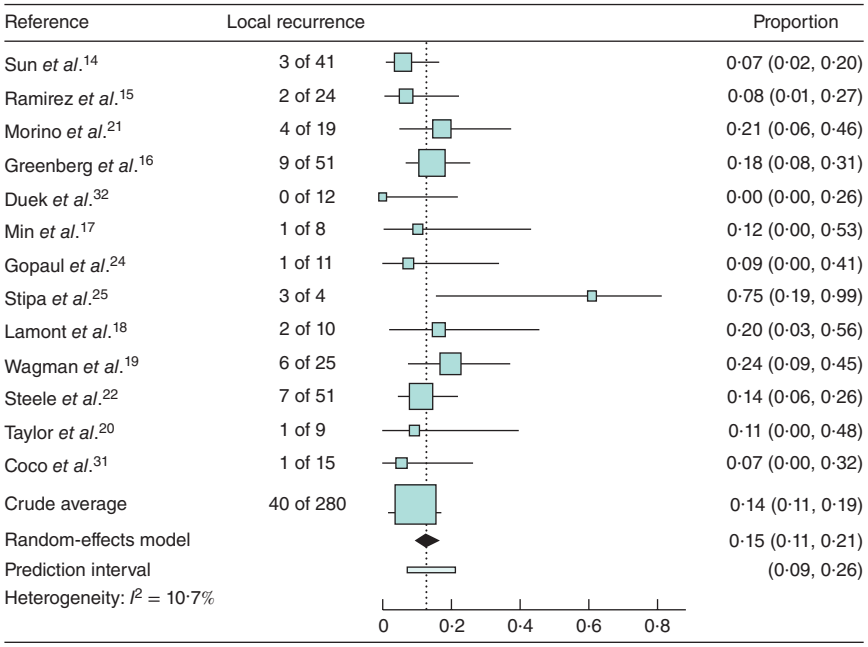


Fig. 2 Forest plots of local recurrence following local excision (transanal excision or transanal endoscopic microsurgery) combined with adjuvant (chemo)radiotherapy in patients with **a** pT1–pT2, **b** pT1 and **c** pT2 adenocarcinoma. An inverse-variance random-effects model was used for analysis. Proportions are shown with 95 per cent confidence intervals. *Fig. 2* continues on next page

studies. The primary outcome was assessed for combined pT1–2 categories, as well as for pT1 and pT2 categories separately.

For each defined subgroup according to treatment modality and pT category, a weighted average of the proportions was determined by means of the generic inverse-variance method. This is a method for aggregating multiple effect sizes to minimize the variance of the weighted average, giving more weight to the effect of large studies than to small ones. Heterogeneity was assessed by use of the I^2 statistic. A prediction interval was calculated to present the dispersion of outcomes graphically. Analyses were performed with the inverse-variance method, using a random-effects model. As the inverse-variance method may lead to overestimation in smaller cohorts, crude local recurrence rates for the main study populations and the



C pT2

Fig. 2 continued

different subgroups were also calculated. Subsequently the Wilson score method for single proportions was used to calculate a confidence interval for these crude averages. It was expected that the search would yield mainly small-sized cohorts, which was the reason for providing both weighted averages and crude rates. Analyses were performed with the use of R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Included studies

The process of selection and reasons for exclusion are displayed in *Fig. 1*. Fourteen of the 19 included studies[14–32] were on local excision followed by adjuvant radiotherapy and seven were on completion TME; two studies[17,21] compared both treatment modalities.

Quality assessment of the included studies is summarized in *Figs S1* and *S2* (supporting information). Owing to the strict inclusion and exclusion criteria, the included studies were adequate with regard to length of follow-up and assessment of endpoints, but insufficient for sample size and prospective study design. No randomized studies comparing the two treatment modalities could be identified.

Fourteen cohort studies on local excision with adjuvant (chemo)radiotherapy were selected, including two comparative studies[17,21]. Of a total of 405 patients, 94 (23·2 per cent) had category pT1 disease and 292 (72·1 per cent) had pT2; pT category was not specified for 19 patients (4·7 per cent). Eight studies[17–24] included patients with positive resection margins. Local excision was performed by TEM in five studies[15,21,22,25,32] and by TAE in four[14,18,20,31]; more than one technique was used in three studies[16,19,23], and the method for local excision was not reported in the remaining two[17,24]. The adjuvant treatment consisted of radiotherapy alone in five[14,15,20,31,32] of the 14 studies, chemoradiotherapy alone in four[16,18,21,22], and various radiotherapy schedules with and without concomitant chemotherapy in the remaining five studies[17,19,23–25]. Patient selection for adjuvant (chemo)radiotherapy based on pathological criteria differed between the studies. Detailed baseline characteristics of patients who underwent adjuvant (chemo)-radiotherapy are shown in *Table 1* and *Table S1* (supporting information).

Seven observational cohort studies reported on completion TME after local excision, with a total of 130 patients. Two[17,21] of these seven studies were the previously mentioned comparative studies. Of these 130 patients, 81 (62·3 per cent) had category pT1 disease and 49 (37·7 per cent)

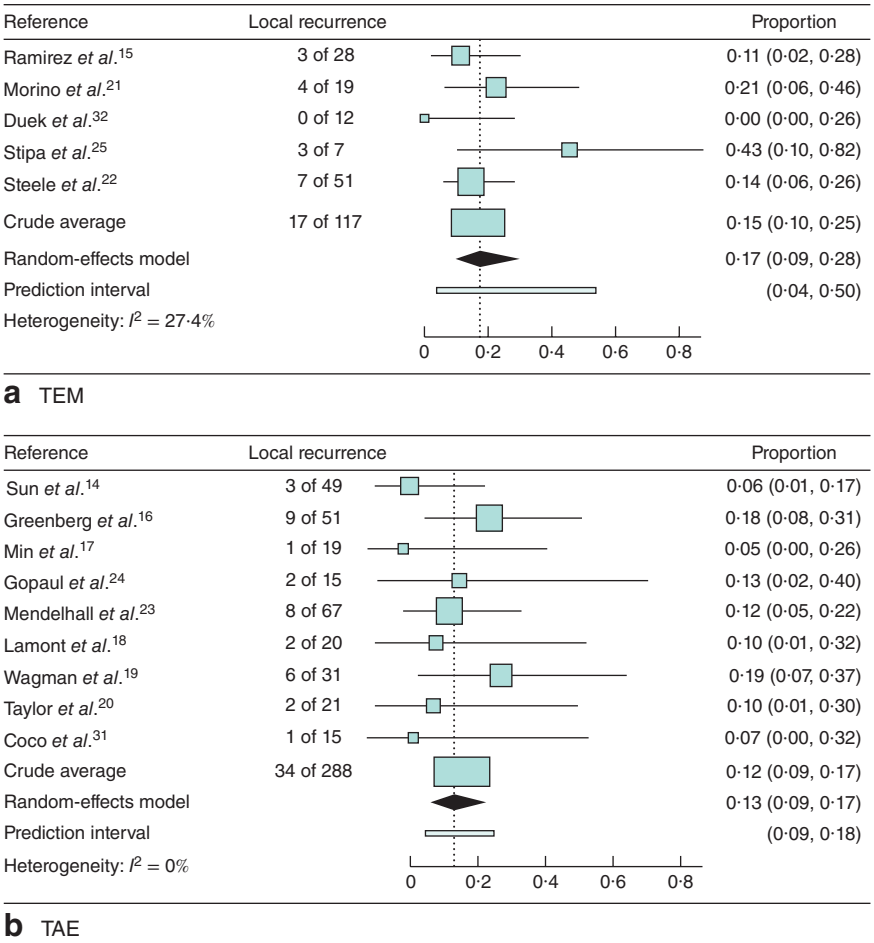


Fig. 3 Forest plots of local recurrence following **a** transanal endoscopic microsurgery (TEM) and **b** transanal excision (TAE), both followed by adjuvant (chemo)radiotherapy in patients with pT1–pT2 adenocarcinoma. An inverse-variance random-effects model was used for analysis. Proportions are shown with 95 per cent confidence intervals

had pT2. Five studies[21,26–29] included patients with positive resection margins. Local excision was performed using TEM in six studies[21,26–30], and the method of local excision was not reported in one study[17]. The study of Nakagoe and colleauges[30] was the only one in which the entire cohort received completion TME; only the subgroups with completion TME were included from the remaining six studies. Detailed characteristics of the cohort studies on completion TME are presented in *Table 2* and *Table S2* (supporting information).

Local recurrence

Local recurrence rates after local excision followed by (chemo)radiotherapy ranged from zero of 12 to three of seven patients for both T categories combined (*Fig. 2*)[25,32]. The crude local recurrence rate for the combined T categories was 51 (12·6 per cent) of 405. The weighted average of the local recurrence rate was 14 (95 per cent c.i. 11 to 18) per cent. The crude local recurrence rate after adjuvant (chemo)radiotherapy was three (5 per cent) of 60 for patients with pT1 and 40 (14·3 per cent) of 280 for those with pT2 cancers, with weighted averages of 10 (4 to 21) and 15 (11 to 21) per cent respectively (*Fig. 2*). A subgroup analysis of TEM *versus* TAE followed by adjuvant (chemo)radiotherapy showed a weighted average of 17 and 13 per cent respectively for pT1–2 combined (*Fig. 3*).

Local recurrence rates after local excision followed by completion TME for the two T categories combined ranged from zero of 37[28] to one of five[21] patients, with an overall crude local recurrence rate of six (4·6 per cent)

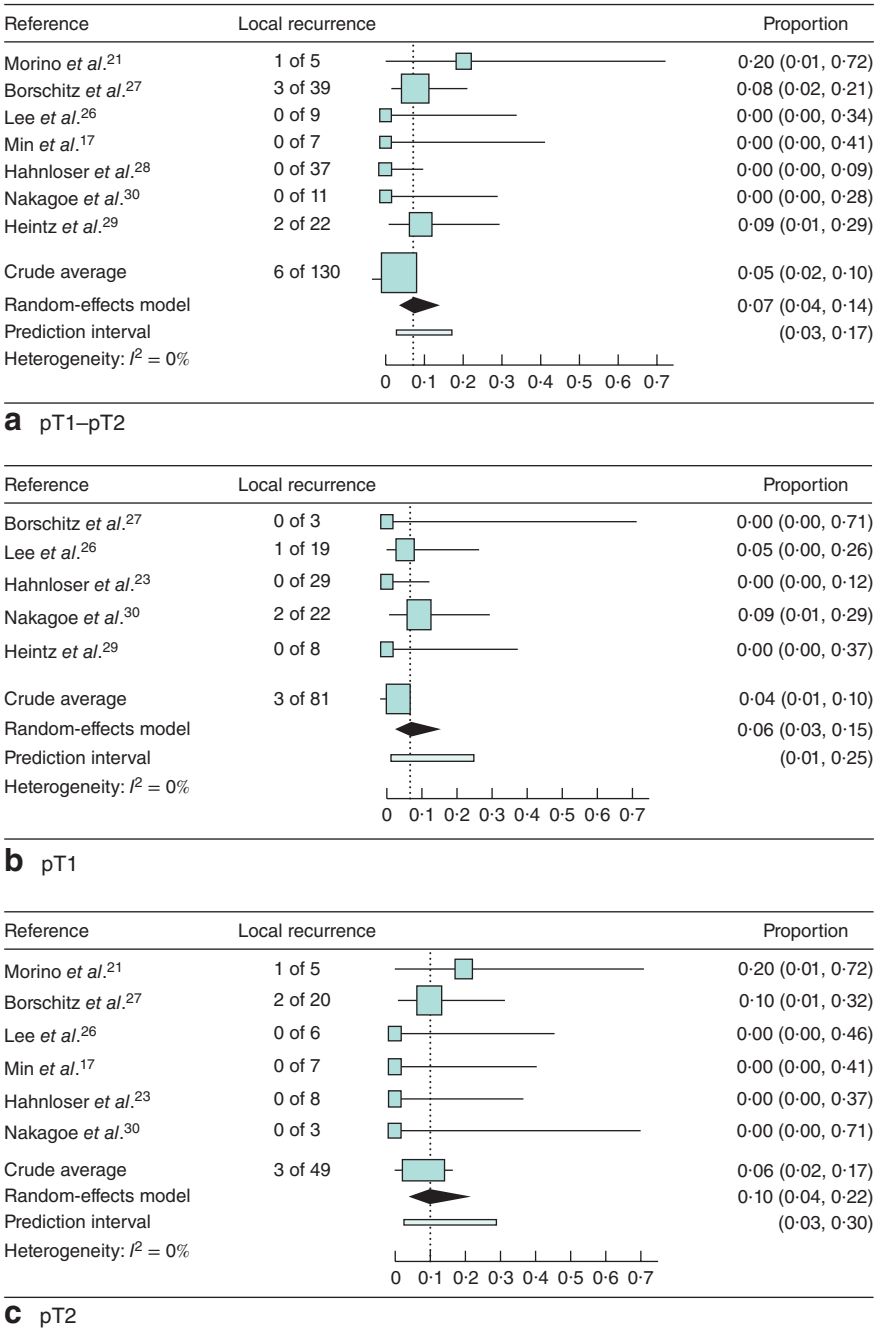


Fig. 4 Forest plots of local recurrence following local excision (transanal excision or transanal endoscopic microsurgery) followed by completion total mesorectal excision in patients with **a** pT1–pT2, **b** pT1 and **c** pT2 adenocarcinoma. An inverse-variance random-effects model was used for analysis. Proportions are shown with 95 per cent confidence intervals

of 130. The weighted average of the local recurrence rate was 7 (95 per cent c.i. 4 to 14) per cent. The crude local recurrence rate after completion TME was lower in patients with pT1 than in those with pT2 disease: three (4 per cent) of 81 *versus* three (6 per cent) of 49 patients. The weighted average of the local recurrence rate was 6 (3 to 15) per cent for pT1 compared with 10 (4 to 22) per cent for pT2 (*Fig. 4*).

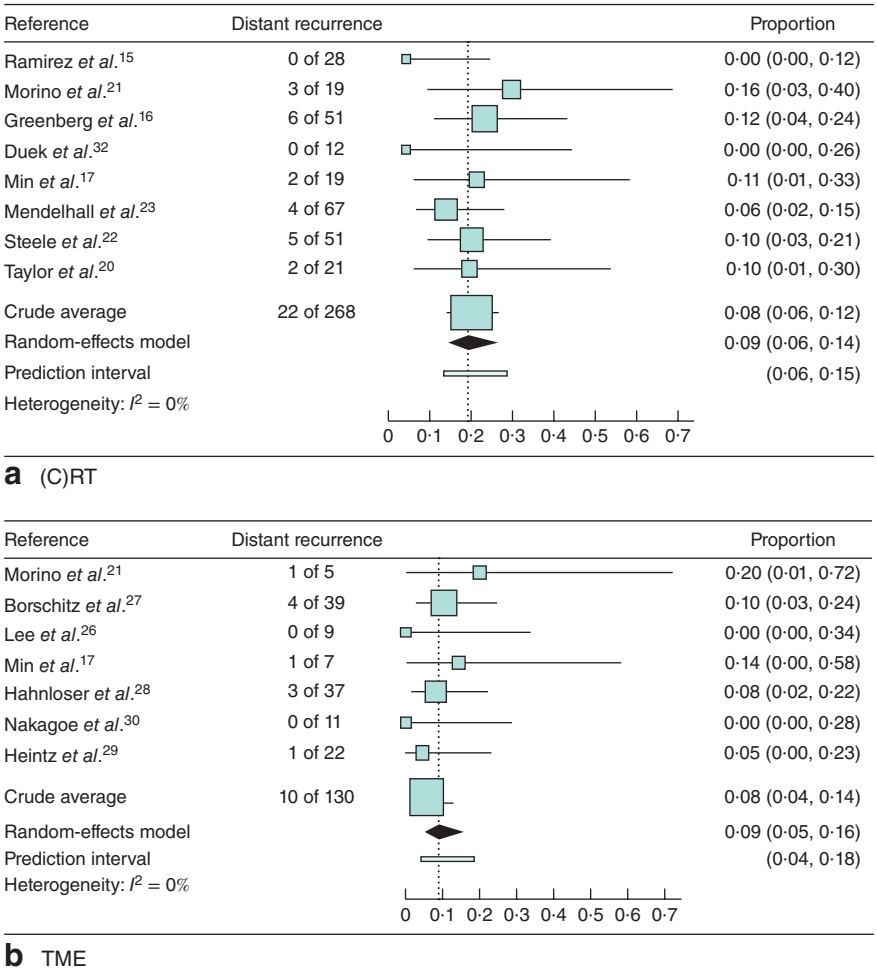


Fig. 5 Forest plots of distant recurrence in patients with pT1–pT2 adenocarcinoma according to treatment modality: **a** local excision plus adjuvant (chemo)radiotherapy ((C)RT) and **b** local excision plus total mesorectal excision (TME). An inverse-variance random-effects model was used for analysis. Proportions are shown with 95 per cent confidence intervals

Distant recurrence

Distant recurrence rates after local excision with adjuvant (chemo)radiotherapy for pT1/pT2 rectal cancer ranged from zero of 28[15] to three of 19[21] patients. Overall, the crude distant recurrence rate was 22 (8·2 per cent) of 268, and the weighted average was 9 (95 per cent c.i. 6 to 14) per cent (*Fig. 5*). After local excision with completion TME, the distant recurrence rate ranged from zero of 11[30] to one of five[21] patients, with an overall crude rate of ten (7·7 per cent) of 130 and a weighted average of 9 (5 to 16) per cent.

Survival

Reported survival data for the two treatment strategies are summarized in *Tables 3* and *4*. Pooling of data was not performed because local excision alone was sometimes included in the overall results, and timing and type of survival analysis varied substantially among the studies. The 5-year OS rate for patients receiving adjuvant (chemo)radiotherapy after local excision was reported in five studies[14,19,23,24,31] and ranged from 61 to 80 per cent. The 5-year DFS rate ranged from 75 to 100 per cent among three studies[17,19,20], and 5-year DSS ranged from 75 to 100 per cent in six studies[15,17,20,23,24,31] (*Table 3*). The 5-year OS rate for patients receiving completion TME after local excision was 79 and 100 per cent in two eligible studies[28,30], and two studies reported a DFS rate of 94 and 86 per cent after 5 and 10 years respectively[27,28] (*Table 4*).

Table 3 Outcome data of local excision with adjuvant (chemo)radiotherapy

Reference	No. of patients	T category	Local recurrence	Distant recurrence	Survival (%)
Sun *et al.*[14]	49	T1: 8 (16) T2: 41 (84)	3 (6): T1, 0; T2, 3 (5 years)	13 of 116 (11·2)‡	5-year OS: 61 (30 of 49) T1: 63 (5 years); 50 (10 years) T2: 61 (5 years); 34 (10 years)
Ramirez *et al.*[15]	30	T1: 6 (20) T2: 24 (80)	3 of 28 (11) (2 lost to follow-up): T1, 1; T2, 2 of 24 (8)	0 of 28 (0)	5-year DSS: 93
Morino *et al.*[21]	19	T2: 19 (100)	4 (21)	3 (16)	n.r.
Greenberg *et al.*[16]	51	T2: 51 (100)	9 (18)	6 (12)	10-year OS: 66 (51, 84)† 10-year DFS: 64 (51, 80)† 10-year DSS: 75 (64, 89)†
Duek *et al.*[32]	12	T2: 12 (100)	0 (0)	0 (0)	3-year OS: 100 3-year DFS: 100
Min *et al.*[17]	19	T1: 11 (58) T2: 8 (42)	1 (5): T1, 0; T2, 1	2 (11): T1, 2; T2, 0	5-year DFS: T1: 100 (11 of 11) T2: 75 5-year DSS: T1: 100 (11 of 11) T2: 75
Gopaul *et al.*[24]	15	T1: 4 (27) T2: 11 (73)	2 (13): T1, 1; T2, 1	6 of 64 (9)‡	5-year OS: 71‡ 5-year DSS: 83‡
Stipa *et al.*[25]	7	T1: 3 (43) T2: 4 (57)	3 (43): T1, 0; T2, 3	4 of 83 (5)‡	n.r.
Mendenhall *et al.*[23]	67	T1: 34 (51) T2: 12 (18) T3: 2 (3) No data: 19 (28)	8 of 67 (12)	4 (6)	5-year OS: 80‡ 5-year DSS: 90‡
Lamont *et al.*[18]	20	T1: 10 (50) T2: 10 (50)	2 (10): T1, 0; T2, 2	3 of 48 (6)‡	DFS: 70
Wagman *et al.*[19]	31	T1: 6 (19) T2: 25 (81)	6 (19): T1, 0; T2, 6	15% abdominal failure; 15% distant failure§	5-year OS: 70‡ 5-year DFS: 77‡
Steele *et al.*[22]	51	T2: 51 (100)	7 (14)	5 (10)	6-year OS: 85 (57, 96)† 6-year DFS: 71 (43, 88)†
Taylor *et al.*[20]	21	T1: 12 (57) T2: 9 (43)	21 (10): T1, 1; T2, 1	2 (10): T1, 1; T2, 1	5-year DSS: 77 5-year DFS: 81
Coco *et al.*[31]	15	T2: 15 (100)	1 (7)	n.r.	5-year OS: 75 5-year DSS: 90

Values in parentheses are percentages unless indicated otherwise; †values in parentheses are 95 per cent confidence intervals. ‡Values for total population. §Abdominal failure: liver, retroperitoneal lymph nodes or peritoneal seeding; distant failure: lung, bone, brain. OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival.

Table 4 Outcome data of local excision with completion total mesorectal excision

Reference	No. of patients	T category	Local recurrence	Distant recurrence	Survival (%)*
Morino *et al.*[21]	5	T2: 5 (100)	1 (20)	1 (20)	n.r.
Borschitz *et al.*[27]	39	T1: 19 (49) T2: 20 (51)	3 (8): T1, 1; T2, 2	4 (10)	10-year DFS: 86 10-year DSS: 89
Lee *et al.*[26]	9	T1: 3 (33) T2: 6 (67)	0 (0)	0 (0)	n.r.; 1 death
Min *et al.*[17]	7	T2: 7 (100)	0 (0)	1 (14)	Patients undergoing TME excluded from survival rates
Hahnloser *et al.*[28]	37	T1: 29 (78) T2: 8 (22)	0 (0)	3 (8): T1, 2; T2, 1	5-year OS: 79 (66, 93) 10-year OS: 62 (46, 80) 5-year DFS: 94 (86, 99) 10-year DFS: 90 (79, 99)
Nakagoe *et al.*[30]	11	T1: 8 (73) T2: 3 (27)	0 (0)	0 (0)	5-year OS: 100
Heintz *et al.*[29]	22	T1: 22 (100)	2 (9)	1 (5)	OS low-risk radical surgery group: 81† OS high-risk radical surgery group: 69†

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Overall survival (OS) also includes patients undergoing primary total mesorectal excision (TME). n.r., Not reported; DFS, disease-free survival; DSS, disease-specific survival.

Discussion

The local recurrence rate appeared to be higher in patients with locally excised pT1/pT2 category rectal cancer treated by adjuvant (chemo)radiotherapy than in patients who underwent completion TME. However, these two patient cohorts are not directly comparable. The relatively high recurrence rate in the pooled adjuvant (chemo)radiotherapy cohorts could be explained by the larger proportion of T2 carcinomas. Furthermore, ten of 14 included studies on adjuvant (chemo)radiotherapy involved patients with a carcinoma larger than 4 cm, which is associated with an increased risk of recurrence[4]. TEM was the more common local excision approach in the completion TME group. Studies have shown that TEM is associated with lower recurrence rates owing to higher rates of clear margins and a lower risk of tumour fragmentation compared with TAE[33]. However, subgroup analysis revealed a similar risk of recurrence after TEM and TAE followed by adjuvant radiotherapy (*Fig. 3*)[34,35]. Bias might exist in favour of the completion group, possibly due to greater experience with the TEM procedure and better follow-up.

Several other characteristics differed among the included cohorts, which hampers interpretation of outcome for each treatment modality. Radiotherapy schedules differed, and a substantial number of patients received radiotherapy alone. From the neoadjuvant setting, it is known that response rates are increased by concomitant chemotherapy, and this is likely to be translatable to the adjuvant setting. Decisions to treat a patient with adjuvant (chemo)radiotherapy were left to the discretion of the physicians and were probably influenced by patient preferences. None of the studies prospectively evaluated a strict treatment protocol with predefined selection criteria based on tumour characteristics. Even when pT category was specified as selection criterion for adjuvant radiotherapy, further risk stratification using other histological characteristics was often lacking. Selection for completion TME was more clearly specified in the identified studies, and seemed to be more consistent. In addition, completion TME studies were all consecutive series, in contrast to the majority of the radiotherapy studies, with the potential risk of introducing allocation bias.

It was decided eventually to perform pooled analyses (the calculated weighted average) of local recurrence for each treatment modality, despite all the methodological issues. This gives more insight than separate results from small individual studies with wide confidence intervals. The weighted averages for the more homogeneous subgroups of pT1 and pT2 categories should be interpreted with caution, for the above-mentioned reasons. Despite all shortcomings, it can be concluded that the local recurrence rate after adjuvant radiotherapy for locally excised early-stage rectal cancer is relatively high, based on the best available evidence to date. Better selection is needed to consider this a valid option for fit patients being treated with curative intent. Additionally, adjuvant radiotherapy may be an acceptable alternative for completion TME in patients with high operative risk.

Further improvement in imaging modalities such as MRI may enable more accurate selection of node-negative tumours for local excision and early detection of locally recurrent disease. When rectum-preserving treatment is applied, a careful follow-up schedule using digital rectal examination, endoscopy and imaging should be followed for timely detection of local recurrences, which enables effective salvage surgery. This will lead to a better outcome, as early salvage therapy is associated with an acceptable oncological outcome[11]. In seven of the 14 included studies on adjuvant radiotherapy, no strict follow-up protocol was reported.

Local excision alone for high-risk T1 and low-risk T2 rectal carcinomas is generally not accepted, because it is associated with an unacceptable risk of recurrence in comparison with TME surgery owing to outgrowth of (micro)metastases in the mesorectum or residual disease in the excision bed. De Graaf and colleagues[1] reported a local recurrence rate of 24 per cent after TEM without adjuvant therapy, compared with 0 per cent following TME for pT1 rectal cancer. Rectum-preserving approaches should therefore be tailored to carefully selected patients based on pathology-based risk profiles, in order to prevent curable disease from being treated inadequately.

Based on this systematic review, it is not possible to conclude that patients with locally excised pT1/pT2 rectal cancer can be safely treated with adjuvant (chemo)radiotherapy. Completion TME should still be considered the standard of care after local excision or endoscopic resection of high-risk pT1 and pT2 rectal cancer. However, adjuvant radiotherapy in selected patients with intensive follow-up and early salvage of recurrence could be investigated as a less invasive treatment strategy compared with completion TME in well designed prospective studies. Such a randomized trial has been initiated by the authors and started accrual in the autumn of 2015.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search details (Word document)

Fig. S1 Quality assessment according to the Methodological Index for Non-Randomized Studies (MINORS) checklist (Word document)

Fig. S2 Graphical representation of the Methodological Index for Non-Randomized Studies (MINORS) checklist (Word document)

Table S1 Baseline characteristics of studies on local excision and adjuvant (chemo)radiotherapy (Word document)

Table S2 Baseline characteristics of studies on local excision and completion transanal excision (Word document)