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Transanal Endoscopic Microsurgery (TEM) for Early Rectal Cancer

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Abstract

Aim

To determine the efficacy and safety of TEM compared to radical surgical resection (RSR) in patients with early rectal cancer.

Methods

A meta-analysis was performed following a search of the Pub Med, EMBASE and Cochrane Central Register of Controlled Trials databases. Only randomised controlled trials comparing TEM and RSR were considered for inclusion.

Results

Four trials with a total of 363 patients with early rectal cancer were included. There was no difference in over-all survival (OR 0.93; 95% CI), in rectal cancer-specific survival (OR 1.08; 95% CI), or for distant metastasis (OR 0.86; 95% CI) between the two groups. There was shorter length of hospital stay (OR -3.28; 95% CI), shorter operating time (OR -81.82; 95% CI), less blood loss (OR -138.70; 95% CI) and fewer post-operative complications (OR 0.30; 95% CI) in the TEM group. However local recurrence rate was higher in the TEM group compared to RSR.

Conclusion

This study has shown that in patients with early rectal cancer, TEM does offer oncologic control comparable to RSR and is associated with shorter hospital stay, less operating time, less blood loss and less post-operative complications. However, there appears to be a higher rate of local recurrence that warrants further study.

Introduction

Colorectal cancer (CRC) is considered as one of the leading causes of cancer death in developed countries and causes significant morbidity and mortality resulting in a large global economic burden. Geographical incidence varies, with around 60% of cases occurring within developed countries and it is the 4th and 3rd most common cause of cancer deaths in men and women respectively.[1] In Europe, at least one third of colorectal cancers are located in the rectum, causing 15 to 25 cases per 100,000 inhabitants per year and although colon and rectal cancer share similar features there is a distinct difference in clinical presentation and management approach.[2] The prognosis is very much dependent on the stage of the CRC at the time of the diagnosis and the Royal College of Pathologists recommends that the 5th edition of the TNM staging system is used for colorectal cancer reporting at a national level.[3,4]

The conventional surgical treatment for cancer of the rectum are associated with a high morbidity and poor long-term functional outcomes with postoperative mortality rates ranging from 2% to 6%. Postoperative complications, such as neurogenic bladder, sexual dysfunction, faecal incontinence along with the psychological and social consequences of a colostomy, have been reported at 30% to 46%.[5, 6]

Given the significant complications from RSR, transanal local excision of early rectal cancer is became an attractive alternative as it is associated with less postoperative pain and a shorter length of hospital stay. Furthermore, newer methods such as TEM or transanal minimally invasive surgery (TAMIS) have been introduced that provide better visualization of tumours in the mid and upper rectum.[7]

The aim of this study was to compare transanal local excision, via TEM, with RSR in terms of oncologic control (survival and recurrence) and safety (intra & postoperative complications) in adult patients with early rectal adenocarcinoma (T1 - T2 N0 M0).

Methods

A systematic review was performed in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions.[8-10] We only included randomised controlled trials (RCTs) and included studies had trial participants with early rectal cancer, (T1-T2, N0, M0) defined as lesions limited to the bowel wall with no disease extension beyond the submucosa (T1) or the muscularis mucosa (T2). Furthermore, there was no evidence of lymph node spread (N0) on pelvic MRI and/or Endo-Rectal Ultrasound (ERUS), no distal metastasis (M0) and patients were 18 years of age or older. The intervention assessed was conservative management in the form of TEM which was compared to conventional radical surgical resection in form of open anterior resection, laparoscopic anterior resection, abdominal perineal resection with or without Total Meso rectal Excision (TME).

The primary outcome was overall survival and secondary outcomes were rectal cancer-specific survival, local recurrence, distant metastases, length of hospital stay, operating time, intra-operative blood loss and post-operative complications.

All studies were at least one-year duration for follow-up of outcomes and there were no restrictions by type of setting or by languages of publication.

We designed a comprehensive search strategy with support from a medical librarian, a rigorous search of the literature supplemented by hand searching and retrieval of any additional articles meeting eligibility criteria was done:

Electronic searches of the following databases were performed:

MEDLINE / Pub Med (OVID interface, 1948 onwards).
EMBASE (OVID interface, 1980 onwards).
Cochrane Central Register of Controlled Trials (Wiley interface, current issue).
Grey literature databases: Open SIGLE (http:// opensigle.inist.fr/).

Other sources searched were as follows:

Dissertations and theses databases: Pro Quest Dissertations & Theses Database.
Conference abstracts or proceedings databases (ISI Proceedings).

The literature search was limited to human subjects without any date of publication restriction and the most recent search was performed on May 15, 2018.

Two reviewers independently identified the trials for inclusion by screening the titles and abstracts, according to the 2010 CONSORT Statement for RCTs.[11] We sought full-text articles for any references that at least one of the reviewers identified for potential inclusion. We selected the trials for inclusion based on the full-text articles and to enhance sensitivity, records were removed only if both reviewers excluded the record at the initial screening level. The flow diagram in Figure 1 describes the inclusion and exclusion process.

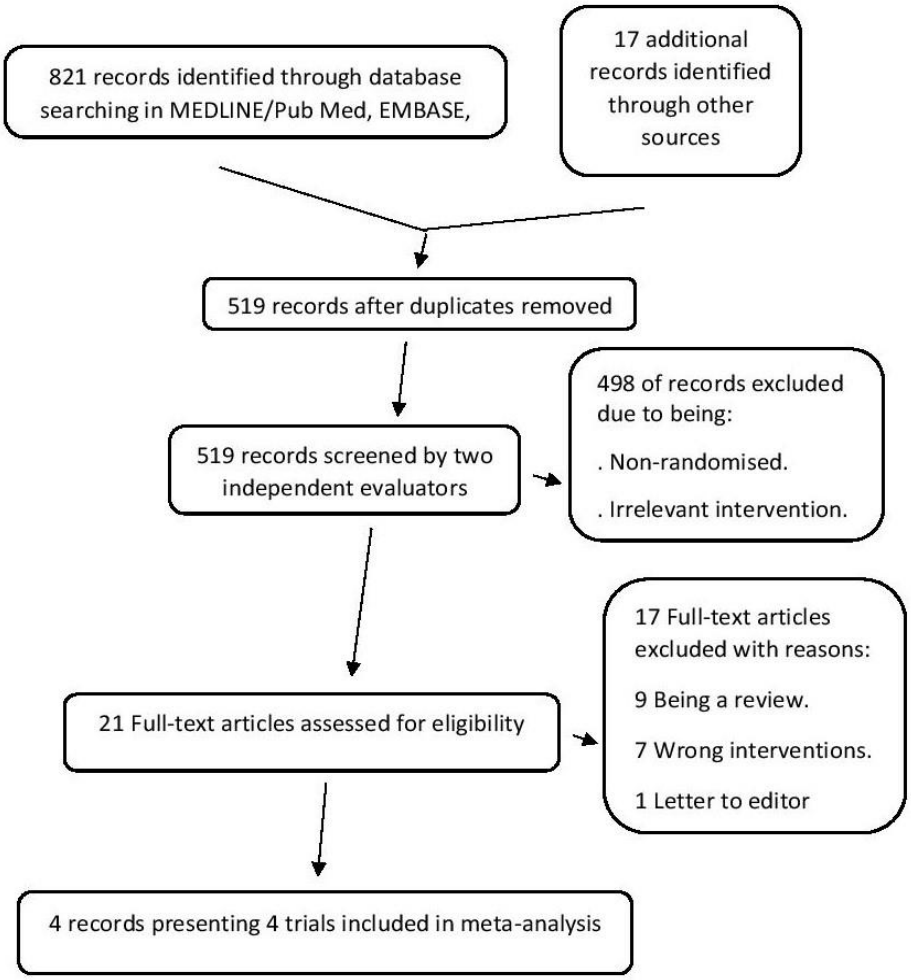

Figure 1: Study Flow Diagram.

Literature search results were processed in Microsoft Excel and we extracted data relating to patients with early rectal cancer, transanal local excision, or radical surgical resection. Two authors independently assessed the risk of bias and evaluated the quality of randomised controlled trials included in the systematic review and meta-analysis using a modified version of the Cochrane Collaboration's Risk of Bias tool. A modified version of the Newcastle-Ottawa Scale and the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) [12] for factors considered included the quality of the random sequence generation and allocation concealment, incomplete outcome data, blinding (participants, personnel and outcome assessors), selective outcome reporting and other risk factors.

With regard to measurement of treatment effect for dichotomous variables (e.g., Overall survival, Rectal cancer-specific survival, Local recurrence or Distant metastasis), we calculated the odds ratio (OR) with 95% confidence intervals (CI). For continuous variables (e.g., Length of hospital stay, Operating time, Blood loss or Post-operative complications), we calculated the mean difference with 95% CI.

Results

The database and other sources searches identified 838 references which were reduced to 519 after duplicates were removed. These references were screened by two reviewers according to the criteria defined above, and we excluded 498 references as non - randomised or irrelevant intervention. The full texts of the remaining 21 references were obtained. Seventeen were excluded and four trials included, involved 363 participants. Their Characteristics are reported in Table 1.

Table 1: Characteristics of included studies.

RCT Randomised control trial, (I) Intervention group, (C) Comparison group.
M: Male, F: Female. TEM Transanal Endoscopic microsurgery.

Study (Year)	Type of study	Study period	Country	Participants	(I) group (n)	(C) group (n)	Mean age in years (Range)		M: F ratio	
							(I)	(C)	(I)	(C)
Winde. (1996)[13]	RCT	1984–1992	Germany	T1N0M0	24	26	63.7 (36-90)	60.9 (47-81)	0.7	1.2
De Graaf. (2009)[14]	RCT	1996-2001	Netherland	T1N0M0	80	75	71 (44-92)	67 (48-83)	23:48	27:48
Lezoche. (2012)[15]	RCT	1997–2004	Italy	T2N0M0	50	50	66 (58-70)	66 (60-69)	30:20	34:16
Chen. (2013)[16]	RCT	2008–2010	China	T1, T2N0M0	28	30	68.8 +/-5-3	66.2 +/- 7-7	14/16	17/13

Study (year)	Outcomes
Winde et al. (1996)	Mortality, early and late morbidity, operative time, blood loss, hospitalization time, post-operative pain and survival rate.
De Graaf EJ et al. (2009)	Morbidity, mortality, margin status, local recurrence, distant recurrence, overall survival and cancer-specific survival.
Lezoche et al. (2012)	Oncological failure, death from rectal cancer after min 5Y follow up, morbidity, 30 days mortality, operative time, blood loss, analgesic use and hospital stay
Chen et al. (2013)	Surgical morbidity and mortality, operative time, blood loss, conversion rate, post-operative recovery time and local recurrence.

Survival Rate

The period of follow-up in these trials varied between 18 and 127 months and the four trials reported no statistically significant differences in over-all survival between the two groups (TEM group: 13/182) vs (RSR group: 11/181); OR 1.55 [0.53, 4.54], (95% CI), Heterogeneity: $Chi^2 = 1.34$, df = 2 (P = 0.51); $I^2 = 0\%$, Test for overall effect: Z = 0.80 (P = 0.43), (Figure 2). Also, the four trials reported no statistically significant differences in rectal cancer – specific survival between the two groups (TEM group: 10/182) vs. (RSR group: 9/181); OR 1.08 [0.44, 2.67], (95% CI), Heterogeneity: $Chi^2 = 0.86$, df = 2 (P = 0.65); $I^2 = 0\%$, Test for overall effect: Z = 0.17 (P = 0.87), (Figure 3).

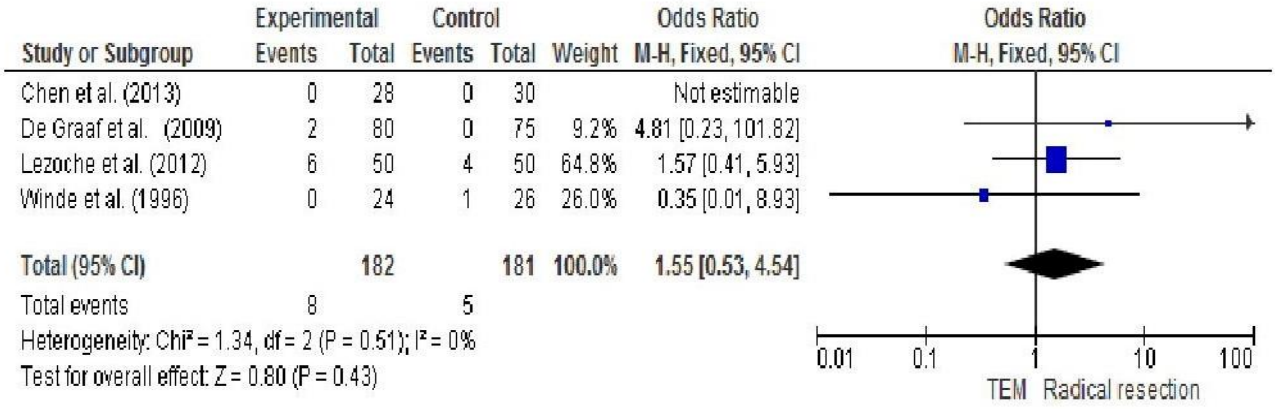

Figure 2. Forest plots comparing over-all survival of TEM versus Radical resection. CI=confidence interval, TEM=Trans anal Endoscopic Microsurgery, OR=odds ratio.

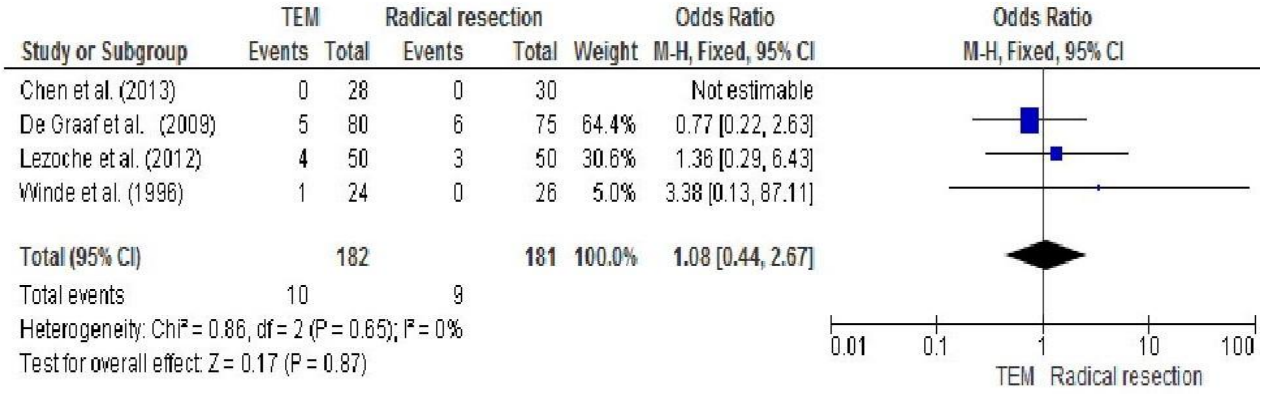

Figure 3. Forest plots comparing rectal cancer – specific survival of TEM versus Radical resection. CI=confidence interval, TEM=Trans anal Endoscopic Microsurgery, OR=odds ratio.

Recurrence

In one study, (De Graaf et al. 2009),[14] fifteen participants (24%) in the TEM group versus none in the RSR group had local recurrence at median follow-up of 42 and 84 months for TEM and RSR group respectively, (P = 0.00001).

Results of the other three studies showed no statistically significant differences between the two groups (TEM group: 7/102) versus (RSR group: 3/106) in relation to local recurrence.

When all four trials were analysed in a forest plot, De Graaf et al. 2009,[14] with the largest number of participants (155 patients) has driven the results to record TEM as being associated with high local recurrence rate in comparison to RSR group; OR 5.59 [2.01, 15.53], Heterogeneity: $Chi^2 = 4.92$, df = 3 (P = 0.18); $I^2 = 39\%$, Test for overall effect: Z = 3.30 (P = 0.001).

For distant metastasis, Results of all four studies showed no statistically significant differences between groups (TEM group: 8/182) vs (RSR group: 9/181); OR 0.86 [0.33, 2.23], Heterogeneity: $Chi^2 = 0.34$, df = 2 (P = 0.84); $I^2 = 0\%$, Test for overall effect: Z = 0.32 (P = 0.75).

Length of Hospital Stay

There were significant reductions in the length of hospital stay between the TEM group and RSR group, OR -3.28 [-3.43, -3.12], Heterogeneity: $Chi^2 = 270.92$, df = 3 (P < 0.00001); $I^2 = 99\%$, Test for overall effect: Z = 42.43 (P < 0.00001).

Operating time

The TEM group in all four studies had a significantly shorter operating time compared to RSR group, OR -81.85 [-83.90, -79.80], Heterogeneity: $Chi^2 = 117.76$, df = 3 (P < 0.00001); $I^2 = 97\%$, Test for overall effect: Z = 78.20 (P < 0.00001).

Blood Loss

The TEM group in all four studies had significantly less blood loss compared to the RSR group, OR -139.24 [-153.02, -125.24], Heterogeneity: $Chi^2 = 807.79$, df = 1 (P < 0.00001); $I^2 = 100\%$, Test for overall effect: Z = 19.81 (P < 0.00001). In two studies, no patient in TEM group received blood transfusion, whereas ten (20 %) in the RSR group had blood transfusion (P<0.001), and one patient (3.3 %) in the RSR group had blood transfusion (P=1.000), in Lezoche et al. (2012)[15] Chen et al. (2013)[16] respectively.

Post-operative complications

The TEM group in general, were associated with less post-operative complications compared to the RSR group. 3 trials showed less, but not statistically significant, post-operative complications with the TEM group (Winde et al. (1996)[13] Lezoche et al. (2012)[15] Chen et al. (2013)[16]), OR 0.70 [0.35, 1.38], Heterogeneity: $Chi^2 = 0.76$, df = 2 (P = 0.68); $I^2 = 0\%$, Test for overall effect: Z = 1.03 (P = 0.30). One trial (De Graaf et al. (2009) [14]) had significantly less post-operative complications compared to the RSR (TEM group: 5/80) vs (RSR group: 48/75); (P < 0.00001).

Discussion

Well-conducted randomised trials investigating TEM are scarce. All included RCTs compared TEM as intervention to RSR for patients with T1 or T2, N0 M0 rectal cancer, and reported our primary outcome 'overall survival'. The study by Chen et al. 2013[16] had a short follow-up (18 to 21 months) compared to the other three trials (45 to 65 months). However, it is remarkable that these studies comparing TEM, to other forms of conventional RSR showed no significant differences on overall survival in both treatment arms.

Also, all included studies reported most of our secondary outcomes, study results showed that TEM is comparable to conventional RSR, in appropriately selected early rectal cancer patients, in relation to rectal cancer-specific survival, local recurrence and distant metastasis. They also showed favourable results in length of hospital stay, operating time, blood loss and post-operative complications.

However, in relation to local recurrence, the results of three studies (Winde 1996[13], Lezoche 2012[15] and Chen 2013[16]) showed no statistically significant differences between the two groups (TEM group: 7/102) versus (RSR group: 3/106). When all four trials were analysed in a forest plot De Graaf et al. 2009 [14] with the largest number of participants (155 patients) has driven the results to record TEM as being associated with a high local recurrence rate in comparison to the RSR group. Adjuvant or neo-adjuvant radiotherapy with or without the addition of chemotherapy have been reported in this context, with variable results. There are no current guidelines recommending radio-chemotherapy for T1-T2 node-negative rectal tumours. Also, patients with local recurrence still can go for salvage surgery, without need for multivisceral resections and without adding a significant postoperative mortality.

No study from the four studies included in this review has mentioned that if the local recurrence was luminal or nodal.

Our review included four randomised controlled trials with 363 participants. The study samples included in this review are relatively small ranging from 50 to 155 participants. In general, there was no evidence of heterogenicity in most comparisons with the exception of the local recurrence in the comparison TEM versus conventional RSR, only in one study (De Graaf et al. 2009).[14]

We agreed with several systematic reviews and meta-analysis, mainly for non-randomised prospective studies, as this is the first systematic review and meta-analysis including only randomised controlled studies, that showed that, for patients with T1 and T2 rectal cancer, the overall survival, rectal cancer-specific survival and distant metastasis did not differ between the TEM and RSR groups (Lu J-Y 2015[17], M. S. Sajid 2013[18]).

Our results agree with several systematic reviews and meta-analysis that in selected cases of early rectal cancer, TEM is superior to standard RSR concerning length of hospital stay, operating time, blood loss and post-operative complications especially need for stoma and anastomotic leakage (Sgourakis G 2010[19], Kidane B 2015[20]).

The present review has a number of limitations. Two of the included trials presented their results with some missing original data, and we failed to get a response from authors regarding this, so we estimated the mean and standard deviation instead. Also, one of the flaws of this review is the combined analysis of trials with and without the use of neoadjuvant chemotherapy or chemo radiotherapy.

In conclusion, in selected Patients with early rectal cancer (T1 - T2 N0 M0), TEM does offer oncologic control comparable to conventional RSR in terms of overall survival, rectal cancer-specific survival and distant metastasis. TEM is associated with lower length of hospital stay, operating time, blood loss and post-operative complications.

However, regarding local recurrence, our meta-analysis has clearly shown an increase in local recurrence for patients receiving local resection alone compared to RSR.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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