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Title: Neoadjuvant short-course radiotherapy for upper third rectal tumors: a systematic review and individual patient data meta-analysis of randomized controlled trials

Running head: Radiotherapy for upper third rectal tumors

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SYNOPSIS

Meta-analysis to compare oncological outcomes with neoadjuvant radiotherapy and surgery versus surgery alone for upper third rectal tumors using individual patient data from randomized controlled trials identified no significant benefit conferred by neoadjuvant radiotherapy for local recurrence, overall survival or disease free survival in patients undergoing curative surgery for upper third rectal cancer. Surgery alone for patients with potentially curative disease at preoperative staging may be sufficient in selected cases.

ABSTRACT

BACKGROUND: There is no consensus on the use of neoadjuvant radiotherapy for tumors of the upper third of the rectum. Due to the conflicting findings of high quality trials and given the significant long term side effects associated with neoadjuvant radiotherapy, the benefit of neoadjuvant radiotherapy for upper third rectal tumors is less certain than for lower two third rectal tumors. This meta-analysis compares oncological outcomes with neoadjuvant radiotherapy and surgery versus surgery alone for upper third rectal tumors.

METHODS: Pubmed, Embase and the Cochrane library databases were searched. Randomized controlled trials (RCT) comparing neoadjuvant radiotherapy and surgery versus surgery alone for resectable rectal cancer were included. Individual patient data were sought from the principal investigator of each eligible trial for comparative data on patients with upper third rectal tumors. The main outcomes measured were survival outcomes, oncological outcomes, post-operative morbidity and late toxicity.

RESULTS: Individual patient data from two RCTs examining outcomes in 758 patients were obtained. Published data from one further RCT containing comparable data on upper third rectal tumors was included in analysis of local recurrence. In patients with curative surgery there was no significant reduction in local recurrence and no significant improvement in overall survival or disease-free survival with neoadjuvant radiotherapy (LR RR: 0.38, 95% CI: 0.14 to 1.04, p=0.06) (OS RR: 1.10, 95% CI: 0.98 to 1.24, p=0.11) (DFS RR: 1.11, 95% CI: 0.97 to 1.26, p=0.13).

CONCLUSIONS: The benefit of neoadjuvant radiotherapy for upper third rectal tumors is not certain, and surgery alone for patients with potentially curative disease at preoperative staging may be sufficient.

INTRODUCTION

Neoadjuvant radiotherapy in conjunction with total mesorectal excision (TME) improves rates of local recurrence for rectal cancer (1, 2). Combined data for all rectal cancer locations have been used in the analysis of randomized controlled trials (RCTs) (1, 2). Upper third tumors represent a different entity as they are frequently located above the peritoneal reflection where only the posterior mesorectal plane is present. As with rectosigmoid tumors, upper third tumors above the peritoneal reflection may not benefit from the tumor downstaging afforded by neoadjuvant radiotherapy and therefore can potentially avoid the acute and delayed toxicity associated with this treatment (3).

The rectum is typically divided into discrete segments: upper, middle and lower thirds. Definitions of distances defining these segments vary internationally resulting in clinical trials with conflicting definitions and inconsistent guidelines regarding management of rectal cancer (4). An international panel of experts recently agreed the sigmoid take-off as seen on computed tomography (CT) and magnetic resonance imaging (MRI) to define the junction of rectum and sigmoid (4). Tumors which straddle the take-off are classified as rectosigmoid. Upper third rectal tumors are defined as those below the take-off but may be above the peritoneal reflection. The most commonly reported pragmatic definition for the rectum in daily use by experts was ≤15cm from the anal verge (4). A study which measured distance from the anal verge to the anterior peritoneal reflection in vivo found the mean distance to be 11.9cm in males and 10cm in females (5).

Neoadjuvant radiotherapy has the capacity to treat microscopic residual disease beyond or at the edge of the surgical field and reduce the risk of local recurrence (2). The upper third of the rectum above the peritoneal reflection is not enveloped in mesorectum and therefore there is no surrounding anterior or lateral mesorectal fascia (MRF) into which a tumor can invade. Below this, the rectum is fixed in the pelvis and there exists the risk of disease extending beyond the MRF to invade local pelvic structures. Significant evidence suggests neoadjuvant radiotherapy reduces local recurrence and may reduce overall long term mortality (6). Neoadjuvant radiotherapy is associated with increased perioperative morbidity, including wound complications and sepsis, and late toxicity, including sexual dysfunction and fecal incontinence (7, 8). With improvements in surgical technique, most notably the widespread adoption of TME, and the improved accuracy of preoperative local staging, the risk of local recurrence has reduced.

Two major trials have compared neoadjuvant radiotherapy to surgery alone, in which the majority of patients underwent TME; the MRC CR07 trial and the Dutch TME trial (1, 2). Conflicting results were seen regarding the benefit of neoadjuvant radiotherapy for upper third rectal tumors in these studies. Opinions are divided regarding the use of neoadjuvant radiotherapy for upper third rectal tumors due to the conflicting findings of high quality trials. To address this, we performed a systematic review and individual patient data (IPD) meta-analysis of RCTs to compare the effect of neoadjuvant radiotherapy and surgery to surgery alone on survival and oncological outcomes, perioperative morbidity and late toxicity for patients with upper third rectal tumors.

MATERIALS AND METHODS

Overview

Comparative data for upper third rectal tumors in all outcomes of interest were not published in reports from RCT publications. This study was based on IPD obtained from the authors of the original trials combined with published data from one further trial. This study is reported in accordance with the Preferred Reporting Items for a Review and Meta-analysis of Individual Participant Data (9).

Eligibility Criteria

Trials were required to compare the effect of neoadjuvant radiotherapy and surgery versus surgery alone on survival in randomly allocated groups. Eligible trials had to include patients with resectable rectal cancer. Studies in which tumor height was not reported were excluded. In cases where tumor height subgroup data was not reported, trial investigators were contacted to provide raw trial data. We included trials published since Jan 1, 1990, as continuous progress in radiotherapy techniques has resulted in considerable improvement in radiation toxicity and associated morbidity. There were no language restrictions. From the included trials, any patients missing data for tumor height were not included in the individual patient data meta-analysis.

Literature Search and Study Selection

A comprehensive literature search of Pubmed, Embase and the Cochrane Library was conducted to identify all published RCTs that compared neoadjuvant radiotherapy and surgery versus surgery alone in patients with resectable rectal cancer by using the following

in the search algorithm: (rectal) AND (surgery) AND (radiation OR neoadjuvant OR radiotherapy). The latest search was performed on November 21, 2020. Two authors (M.F. and C.C.) independently examined the title and abstract of citations, and the full texts of potentially eligible studies were obtained. The reference lists of retrieved articles were further screened comprehensively for additional eligible publications.

Data Collection

The principal investigator of each eligible trial was contacted to request IPD in anonymized electronic datasets. Each trial was re-analyzed to check data and ensure reproducibility of results, in collaboration with each trial statistician and principal investigator. After evaluating data consistency and completeness and for risk of bias assessment, we validated the results of each trial. Each database was updated with unified coding across trials and merged into a single database. Studies that only had aggregate data from published subgroup analyses available were included for aggregate data analysis. Two authors (M.F. and C.C.) independently assessed the risk of bias of each included trial with the updated version of the Cochrane Risk of Bias Tool (10). We evaluated risk of bias arising from the randomization process, due to deviation from the intended intervention, due to missing outcome data, in measurement of the reported outcome, and in selection of the reported result.

Outcomes

The primary outcome was local recurrence in neoadjuvant radiotherapy vs. direct to surgery groups. Secondary outcomes were overall survival, disease-free survival,

postoperative morbidity, and radiotherapy toxicity. Disease-free survival was defined as the time from randomization to confirmed local recurrence, distant metastases, or death from any cause, whichever occurred first. The following information regarding each eligible trial was recorded: author's names, journal, year of publication, study type, definition of upper rectum, enrolment dates, median follow-up, patient demographics, tumor characteristics, radiotherapy protocol, the use of adjuvant chemotherapy and total number of patients with upper third rectal tumors included. Separate subgroup analyses were planned for those with non-stage IV disease (i.e. excluding those with unresectable disease at diagnosis who would likely have been identified with current staging modalities) and those with negative CRM (>1mm) as determined by histopathological assessment. Patients with a positive CRM received adjuvant treatment and so were excluded from analysis to limit the confounding effect of postoperative chemoradiotherapy on survival and oncological outcomes. Earlier trials included patients with extensive pelvic disease identified at the time of surgery. These patients do not represent a curative cohort and would fit into a separate treatment algorithm. In the modern era these patients would likely have been identified with pre-operative MRI. Subgroup analysis of patients who had a negative CRM and no distant metastasis at the time of surgery was used to best represent a cohort of patients undergoing curative surgery by current standards.

Data Analysis

Statistical analyses for all outcomes of interest were conducted using IPD, on an intention-to-treat basis. Treatment effects were expressed as risk ratios (RRs) for binary outcomes and hazard ratios (HRs) for time-to-event outcomes. All RRs and HRs have been calculated

in relation to the neoadjuvant radiotherapy group to show the risk/hazard associated with this treatment compared to surgery alone. Hazard ratios were calculated using the Kaplan-Meier log rank test and Mantel-Haenszel estimator. Each trial using IPD was first analyzed separately, before combining them using a random-effects meta-analysis model to account for variability between trials. Heterogeneity was evaluated by I^2 and C^2 based Cochran Q statistic test in which $P<0.05$ is taken to indicate the presence of significant heterogeneity (11). Due to the low number of trials, sensitivity analysis could not be conducted. All analyses were conducted using STATA statistical software (version 16.0, Stata Corporation, College Station, TX).

RESULTS

Eligible studies

From the 1077 studies identified in our search, 279 duplicates were removed, and 798 studies were screened for eligibility. After full-text reviews, 3 trials (1, 2, 12) including total of 1001 participants with upper third rectal tumors were eligible for inclusion in the meta-analysis (Figure 1). Individual patient data were obtained from 2 trials (1, 2) (758 patients with upper third rectal tumors). One further trial included aggregate data (243 participants with upper third rectal tumors) (12). Trial and population characteristics and definitions used for the upper rectum are shown in Table 1.

The individual patient data meta-analysis included 758 patients with upper third rectal tumors: 363 (48%) allocated to neoadjuvant radiotherapy and surgery and 395 (52%) allocated to surgery alone. Comparable rates of CRM positivity and stage III disease were observed in both groups. Baseline characteristics of these patients are presented in Table 2. Subgroup analysis of patients with a negative CRM and no distant metastasis at the time of surgery included 288 (75 excluded) in neoadjuvant radiotherapy and surgery group and 299 (96 excluded) in surgery alone group (Table 1).

Primary outcome

Local recurrence

Aggregate data from 3 studies describing 1001 patients included data on local recurrence for upper third rectal tumors. There was a reduced risk of local recurrence with neoadjuvant radiotherapy and surgery compared to surgery alone (RR 0.39 [95% CI 0.16 to 0.93],

p=0.03; Figure 2a). IPD on local recurrence were available from 2 studies describing 758 patients. No significant reduction in local recurrence risk was observed when IPD meta-analysis included patients with a negative CRM and non-stage IV disease (RR 0.38 [0.14 to 1.04], p=0.06; Figure 2b). When only patients with stage IV disease were excluded there was no significant difference in local recurrence (RR 0.25 [0.05 to 1.23], p=0.09; Figure 2c).

Secondary outcomes

Overall Survival

IPD on overall survival were available from 2 studies describing 758 patients. Among the 363 patients allocated to neoadjuvant radiotherapy and surgery, 158 (44%) died compared to 196 (49%) out of 395 patients allocated to surgery alone. Median follow up was 5.2 years. The difference in follow up between trials is outlined in Table 1. There was improved overall survival with neoadjuvant radiotherapy and surgery as compared with surgery alone for upper third rectal cancer (RR 1.13 [95% CI 1.00 to 1.27], p=0.05; Figure 3a). When patients with a positive CRM or stage IV disease were excluded there was no significant difference in overall survival (RR 1.10 [0.98 to 1.24], p=0.11; Figure 3b). When only patients with stage IV disease were excluded there was no significant difference in overall survival (RR 1.11 [1.00 to 1.25], p=0.06; Figure 3c).

Disease-Free Survival

IPD on disease-free survival for upper third rectal tumors were present for two studies (758 patients). There was improved disease-free survival with neoadjuvant radiotherapy and

surgery compared to surgery alone (RR 1.20 [95% CI 1.06 to 1.35], p<0.01; Figure 4a). The improved disease-free survival among patients treated with neoadjuvant radiotherapy and surgery was not observed when analysis included only patients with a negative CRM and non-stage IV disease (RR 1.11 [0.97 to 1.26], p=0.13; Figure 4b). When only patients with stage IV disease were excluded there was a significant improvement in disease-free survival (RR 1.17 [1.04 to 1.32], p=0.01; Figure 4c).

Presented in Table 3 are the hazard ratios of time to event outcomes (LR, OS, DFS) on an intention-to-treat basis and for those who underwent curative surgery (macroscopically complete resection without distant metastases at time of surgery and negative CRM) in MRC CR07 and Dutch TME trials. Subgroup analysis by nodal positivity is presented for those who underwent curative surgery (pN0 vs pN1+).

Postoperative morbidity and late toxicity

IPD on anastomotic leak, intra-abdominal complications, lumbosacral neuropathy and wound failure in upper third rectal tumors was included in two studies (758 patients). Postoperative morbidity data was collected up to 24 months after surgery. There was no significant difference in complication rates or late toxicity between treatment arms (Figure 5-9 available online).

Risk of Bias

All of the studies included in IPD meta-analysis were considered to be at low risk of bias arising from the randomization process, due to deviation from the intended intervention,

due to missing outcome data, in measurement of the reported outcome, and in selection of the reported result.

DISCUSSION

Assessing all patients in an intention-to-treat analysis, patients with upper third rectal tumors when treated with neoadjuvant radiotherapy and surgery have reduced rates of local recurrence and improved overall survival and disease-free survival compared to treatment with surgery alone. However, in patients with a negative CRM and non-stage IV disease, there is no statistically significant reduction in local recurrence and no statistically significant improvement in overall survival or disease-free survival associated with neoadjuvant radiotherapy for upper third rectal tumors. When only patients with stage IV disease are excluded, there is improved disease-free survival but no statistically significant improvement in overall survival and no statistically significant reduction in local recurrence in patients treated with neoadjuvant radiotherapy and surgery compared to surgery alone.

Current evidence from large RCTs regarding neoadjuvant radiotherapy uses combined data of all rectal tumors in analyses of outcomes. Available subgroup analyses from these trials are conflicting. The Stockholm II trial observed a significant reduction in local recurrence in neoadjuvantly irradiated patients with upper third rectal tumors [5 vs 21%; p=0.01] (13). The Swedish Rectal Cancer Trial, which included part of the population of the Stockholm II trial, observed no significant difference in local recurrence in upper third rectal tumors treated with neoadjuvant radiotherapy (12). This is the first study to report oncological outcomes with associated side effects in upper third rectal tumors only, randomized to neoadjuvant radiotherapy and surgery or surgery alone.

In the assessment of survival and oncological outcomes for upper third rectal tumors we must also consider the morbidity and late toxicity associated with neoadjuvant radiotherapy. Postoperative morbidity and long term functional outcomes were worse among irradiated patients in Stockholm II and Swedish Rectal Cancer Trial (7, 14). Patients randomized to neoadjuvant radiotherapy in the Dutch TME Trial had higher rates of intraoperative complications, perineal wound complications, slower recovery of bowel function, increased rates of fecal incontinence and sexual dysfunction, and significantly lower satisfaction with bowel function compared to patients in the surgery alone group (8, 15-17). We did not identify any significant differences in postoperative complications or late toxicity associated with neoadjuvant radiotherapy and surgery compared to surgery alone. This may be explained by the relatively short follow up time period for which we received individual participant data on postoperative complications and late toxicity (2 years) and differences in how postoperative complications and late toxicity events were recorded between the two included trials. The fact that MRC CR07 patients received selective postoperative chemoradiotherapy may have influenced postoperative complication and toxicity outcomes in the surgery alone group however this was not evident from the available short term data. This is likely due to low numbers receiving selective postoperative chemoradiotherapy in the surgery alone group (n=12/112) and the low numbers of events between groups in MRC CR07 (8 vs 8, 0 vs 1, 1 vs 0, and 1 vs 0 for anastamotic leak, intra-abdominal complication, lumbosacral neuropathy and wound failure in neoadjuvant radiotherapy vs surgery alone groups respectively).

In our assessment of the available data we found no statistically significant benefit associated with neoadjuvant radiotherapy regarding oncological outcomes in patients who undergo curative surgery (negative CRM and no distant metastasis at time of surgery) for upper third rectal tumors. While we did not observe any significant increased morbidity or late toxicity associated with neoadjuvant radiotherapy in upper third rectal tumors, the available data from long-term follow up of all rectal cancers would suggest there is significant associated morbidity and late toxicity.

Preoperative staging and TME techniques have greatly improved since the time of MRC CR07 and Dutch trial recruitment resulting in reduced rates of local recurrence. During the MRC CR07 trial, the circumferential resection margin positivity rate decreased ($p<0.001$) and the median distance from the tumor to the circumferential resection margin increased from 5 mm in patients recruited in 1998–99 to 8 mm in those recruited in 2004–05 ($p=0{\cdot}038$) (18). There was a statistically significant reduction in rates of local recurrence in patients who had a negative CRM who received neoadjuvant radiotherapy compared to selective postoperative chemoradiotherapy (CRT) [3.3 vs 8.9%]. The benefit of neoadjuvant radiotherapy is diminished when patients with upper third rectal tumors and a negative circumferential margin are selected out and this effect is seen across both included trials (Table 3). MRI is currently the standard of care for preoperative local staging of rectal cancer. Improved quality of MRI and defined MRI criteria for those at high risk of local or systemic failure have resulted in greater accuracy in identifying tumors at risk of non-curative resection (19).

There are several limitations to our study. Radiotherapy protocols and neoadjuvant strategies have changed significantly since publication of the included trials. Results from studies such as the Stockholm III trial, RAPIDO trial and the uptake of total neoadjuvant treatment have shown promising results in increased rates of pathological complete response and completion of systemic treatments (20-22). The statistical power in the analysis of the subset of patients who have negative CRM and non Stage IV disease represents a significant limitation. The magnitude of the odds ratio in favor of neoadjuvant radiation for the total sample is striking- 0.39. While the statistical significance is lost in the subset analysis on patients with a negative CRM, the Odds Ratio retains its magnitude at 0.38. The sample size for this subset drops significantly by 20% in the neoadjuvant group (n=75/363 patients excluded) and 25% in the surgery alone group (n=96/395 patients excluded). This subgroup analysis may not be sufficiently powered to detect a statistically significant difference in survival or oncological outcomes for patients with a negative CRM however it is difficult to envision additional randomized data becoming available to improve the statistical power. In the Dutch trial, radiotherapy was not associated with an increase in overall survival when the entire trial population was considered. However, for patients with a negative CRM, the two treatment groups differed significantly (p=0.027). This overall survival benefit was not observed in our subgroup analysis of upper third rectal tumors with negative CRM. Furthermore, the MRC CR07 trial routinely offered adjuvant treatment (postoperative CRT or RT) for patients with a positive CRM. Patients treated with adjuvant treatment may introduce a confounding effect on survival and oncological outcomes. Despite attempts to control for differing variables, there is no clear reason for the discrepancy in rates of local recurrence between MRC CR07 and Dutch trials. Staging

modalities for metastatic disease and definitions of the upper extent of the rectum differed (10-15cm versus sacral promontory). Surgical technique may also have differed. Mesorectal excision was mandated in only the Dutch TME trial, however in the MRC CR07 trial 92% of resections were reported as TME. Adjuvant treatment strategies had variability also. Postoperative treatment was allowed in the Dutch TME trial in patients with positive margins. In the MRC CR07 trial, patients with positive margins received concurrent chemoradiotherapy. The use of chemotherapy is a confounding variable in assessing the relative benefit of radiotherapy on oncological outcomes.

Despite limitations, this study is the first to analyze a large dataset of randomized patients with upper third rectal tumors treated with or without neoadjuvant radiotherapy and demonstrates no statistically significant benefit associated with neoadjuvant radiotherapy regarding oncological outcomes in patients with curative surgery for upper third rectal tumors. There is however a statistically significant benefit on the intention-to-treat analysis (LR RR: 0.39, 95% CI: 0.16 to 0.93, p=0.03) (OS RR: 1.13, 95% CI: 1.00 to 1.27, p=0.05) (DFS RR: 1.20, 95% CI: 1.06 to 1.35, p<0.01). The implications for these results are the selective use of neoadjuvant radiotherapy may be offered to patients with upper third rectal tumors at risk of non-curative resection. Upper third rectal tumors that are not locally advanced and at risk of non-curative resection may be treated with surgery alone and avoid the associated morbidity and late toxicity of radiation. This is in agreement with current European society for medical oncology (ESMO) guidelines regarding the selective use of neoadjuvant therapy in locally advanced upper third rectal tumors. The clinical setting has changed since completion of these trials – MRI staging and TME are routine with low rates

of local recurrence. The benefit of radiotherapy for upper third rectal tumors is not certain and surgery alone for patients with potentially curative disease at preoperative staging may be used in selected cases.

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Table and Figure legends

Table 1

Title: Trial and patient characteristics, and definitions used in meta-analyzed trials. Curative surgery denotes patients with macroscopically complete local resection without distant metastases at time of surgery and negative CRM.

*MRC CR07 surgery alone patients with involvement of the CRM received selective postoperative concurrent chemoradiotherapy of 45 Gy in 25 fractions with concurrent 5-fluourouracil.

Legend: RT; radiotherapy, RCT; randomized controlled trial

Table 2

Title: Combined baseline characteristics from randomized clinical trials included in the individual patient data meta-analysis.

*Of patients included in MRC CR07 surgery alone group (n=112), 12 received adjuvent chemoradiotherapy, and 3 received radiotherapy alone.

Legend: RT; radiotherapy, TNM; Tumor Node Metastasis, CRM; Circumferential resection margin

Table 3

Title: Local recurrence, overall survival and disease-free survival on an intention-to-treat basis and for those who underwent curative surgery (macroscopically complete local resection without distant metastases at time of surgery and negative CRM) in MRC CR07

and Dutch TME trials. Stage I/II (pN0) vs Stage III (pN1+) subgroup analysis for those who underwent curative surgery.

Legend: HR; hazard ratio, CI; confidence interval, RT; radiotherapy, TME; total mesorectal excision, ITT; Intention-to-treat, LR; local recurrence, OS; overall survival, DFS; disease-free survival, CRM; Circumferential resection margin

Figure 1

Title: PRISMA-IPD Flow Diagram

Legend: IPD; Individual patient data, PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Figure 2a

Title: Local Recurrence among studies included in the aggregate data meta-analysis. Forest plot shows local recurrence by treatment arm in the intention-to-treat population

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 2b

Title: Local recurrence in those who had curative surgery (macroscopically complete local resection without distant metastases at time of surgery and negative CRM)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 2c

Title: Local recurrence in those who had Stage I-III disease (excluding patients with Stage IV disease only)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 3a

Title: Overall Survival among studies included in the individual patient data meta-analysis. Forest plot shows overall survival by treatment arm in the intention-to-treat population among the overall sample

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 3b

Title: Overall survival in those who had curative surgery (macroscopically complete local resection without distant metastases at time of surgery and negative CRM)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 3c

Title: Overall survival in those who had Stage I-III disease (excluding patients with Stage IV disease only)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 4a

Title: Disease-Free Survival among studies included in the individual patient data meta-analysis. Forest plot shows disease-free survival by treatment arm in the intention-to-treat population among the overall sample

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 4b

Title: Disease-free survival in those who had curative surgery (macroscopically complete local resection without distant metastases at time of surgery and negative CRM)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 4c

Title: Disease-free survival in those who had Stage I-III disease (excluding patients with Stage IV disease only)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 5

Title: Anastomotic Leak

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 6

Title: Anastomotic Leak in those who had curative surgery (macroscopically complete local resection without distant metastases at time of surgery and negative CRM)

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 7

Title: Intra-abdominal complications

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 8

Title: Lumbosacral neuropathy

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Figure 9

Title: Wound failure

Legend: RT; radiotherapy, TME; total mesorectal excision, CI; confidence interval

Author	Journal	Year	Country	Study Type	Enrolment Interval	Follow up (yrs)	Definition upper 1/3	Neoadjuvant RT + Surgery (curative surgery)	Surgery Alone (curative surgery)	Radiotherapy protocol	Adjuvant chemo
Sebag-Montefiore D (1) (MRC CR07/NCIC-CTG CO16)	Lancet	2009	UK + others	RCT	1998-2005	3	>10cm	95 (71)	112 (82)	5x5 Gy + 1 week interval	Select cases*
Van Gijn W (2) (TME trial)	Lancet Oncol	2011	Netherlands+ others	RCT	1996-1999	12	>/=10cm	268 (217)	283 (217)	5x5 Gy + 1 week interval	No
Folkesson J (12) (SRCT)	J Clin Oncol	2005	Sweden	RCT	1987-1990	13	>/=10cm	133	110	5x5 Gy + 1 week interval	No

Table 1

	RT + Surgery n=363	Surgery alone n=395*
Sex (Dutch only) (%)		
Male	165 (62)	183(65)
Female	103 (38)	100 (35)
Type of Surgery (%)		
Anterior Resection	332 (91)	354 (89)
Abdominoperineal excision	5 (1)	7 (1)
Hartmann's	7 (1)	19 (4)
Other	2 (<1)	2 (<1)
None	5 (1)	10 (2)
Missing	12 (3)	3 (<1)
TNM Stage (%)		
0	4 (1)	7 (2)
I	102 (28)	85 (21)
II	102 (28)	122 (31)
III	124 (34)	147(37)
IV	20 (6)	27 (7)
Unknown	11 (3)	7 (2)
CRM involvement (>1mm) (%)		
No	309 (85)	325 (82)
Yes	37 (10)	57 (14)
Unknown	17 (5)	13 (3)

Table 2

	Events/patients		HR (95% CI)	Events/patients		HR (95% CI)
	CR07			**Dutch**		
	RT + TME	**TME**		**RT + TME**	**TME**	
ITT analysis						
LR	1/95	18/112	0.19 (0.08-0.47); p=<0.01	8/268	19/283	0.45 (0.21-0.96); p=0.04
OS	76/95	81/112	0.69 (0.4-1.21); p=0.2	129/268	118/283	0.96 (0.68-1.07); p=0.18
DFS	78/95	76/112	0.52 (0.3-0.9); p=0.02	125/268	112/283	0.93 (0.72-1.21); p=0.5
CRM-						
LR -pN0 -pN1+	1/71 0/43 1/28	8/82 5/49 3/33	0.22 (0.06-0.84); p=0.03 0.14 (0.02-0.80); p=0.03 0.4 (0.06-2.83); p=0.36	6/217 3/152 3/65	12/217 5/143 7/74	0.5 (0.2-1.26); p=0.14 0.57 (0.14-2.28); p=0.42 0.48 (0.14-1.67); p=0.25
OS -pN0 -pN1+	60/71 20/28 40/43	65/82 23/33 42/49	0.71 (0.36-1.44); p=0.35 0.4 (0.11-1.42); p=0.16 0.83 (0.32-2.1); p=0.69	117/217 86/152 31/65	101/217 73/143 28/74	0.82 (0.63-1.08); p=0.15 0.87 (0.62-1.22); p=0.43 0.77 (0.49-1.19); p=0.24
DFS -pN0 -pN1+	58/71 4/43 9/28	64/82 7/49 11/33	0.64 (0.33-1.27); p=0.5 0.61 (0.19-2.0); p=0.41 0.88 (0.37-2.12); p=0.78	115/217 85/152 30/65	96/217 70/143 26/74	0.97 (0.74-1.28); p=0.85 0.99 (0.71-1.36); p=0.95 0.93 (0.54-1.58); p=0.78

Table 3