Comparative Oncologic Outcomes of Upper Third Rectal Cancers: A Meta-analysis

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Abstract

The role for neoadjuvant radiation in upper rectal cancer remains unclear. A meta-analysis of studies comparing outcomes following resection of upper third and distal rectal cancers was performed. The data suggests that upper rectal cancer has reduced local and distant recurrence despite similar disease stage and margin positivity. Upper rectal tumors should be considered a distinct entity to mid and lower rectal tumors.

Introduction: Preoperative radiation combined with mesorectal excision has reduced local recurrence rates in rectal cancer. The role for neoadjuvant therapy in upper third rectal cancer remains unclear. The current study aimed to use meta-analytical techniques to compare outcomes of upper third rectal tumors relative to those of the middle and lower rectum. **Materials and Methods:** Meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Databases were searched for studies comparing outcomes between patients with upper third and more distal rectal cancer undergoing primary resection. Patients receiving neoadjuvant treatment were excluded. Results were reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). **Results:** A total of 174 citations were reviewed; 5 studies comprising 3381 patients were included in the analysis. There was no difference in the rate of T3/4 tumors (OR, 1.303; 95% CI, 0.920-1.847; $P = .137$), lymph node positivity (OR, 1.004; 95% CI, 0.865-1.165; $P = .961$), and circumferential resection margin positivity (OR, 0.898; 95% CI, 0.556-1.450; $P = .660$) between upper third and more distal rectal cancers. However local recurrence (OR, 0.495; 95% CI, 0.302-0.811; $P = .005$) and distant recurrence (OR, 0.613; 95% CI, 0.511-0.734; $P < .001$) were reduced in patients with upper third rectal cancer. **Conclusions:** These data suggest that upper third rectal cancer has reduced local and distant recurrence rates despite similarity in disease stage and margin positivity. Further studies examining effects of neoadjuvant radiation in rectal cancer should consider upper rectal tumors as a distinct entity to middle and lower rectal tumors.

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Introduction

Randomized controlled trials (RCTs) have established that neoadjuvant radiation with or without chemotherapy significantly decreases local recurrence rates in resectable rectal cancer treated with total mesorectal excision (TME).[1,2] The risk of local recurrence increases as the distance between the tumor and anal verge decreases.[3] Interestingly, some studies show no benefit of radiation at the upper limit of the rectum.[4,5]

The rectum can be divided into discrete segments anatomically or by distance from the anal verge. Anatomically, it is most commonly divided into extra-peritoneal and intra-peritoneal. The most common classifications used in randomized trials (TME trial, Swedish Rectal Cancer Trial, Stockholm II) and other published studies are lower, middle, and upper (0-5 cm, 5-10 cm, and 10-15 cm from the anal verge, respectively).[1-3] The majority of anatomical studies report the anterior peritoneal reflection of the rectum to commence close to 10 cm from the anal verge, thus the upper third of the rectum is that which is cephalad to this point.[6] As the upper rectum is not enveloped in mesorectum, and the mesorectal fascia is not always threatened by locally advanced tumors in this area, the benefit of giving neoadjuvant radiation to avoid positive resection margins does not necessarily apply. Current European Society for

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Medical Oncology (ESMO) guidelines define the upper rectum as 10 to 15 cm from the anal verge and recommend preoperative chemoradiation only for T4b upper rectal tumors. For T4a tumors or less, the ESMO guidelines recommend surgery or, in exceptional circumstances, neoadjuvant chemoradiation.[7] Initially large RCTs such as the Dutch TME trial found that there was no benefit in neoadjuvant radiation for upper third tumors; however, a more recent 12-year follow-up study suggests otherwise.[1,4] The Stockholm II trial found that patients with upper rectal tumors significantly benefited from radiation with a reduction in local recurrence; however, a TME technique was not used in all cases. Thus, controversy exists regarding the use of neoadjuvant radiation in upper rectal tumors.

Pelvic irradiation is not without significant short- and long-term side effects. Radiotherapy causes mucosal inflammation and cell death in the short term but leads to persistent cytokine activation leading to progressive ischemia and fibrosis.[8] Gastrointestinal dysfunction such as enteritis and malabsorption can commence immediately. Chronic dysfunction can arise months or even years after treatment.[9] Neoadjuvant radiation is also associated with an increase in sexual dysfunction, secondary malignancies, and stool frequency, limiting daily activities.[10] Given the significant long-term side effects of radiotherapy and a lack of clarity regarding the benefit of radiation for upper third rectal tumors it is important to establish whether or not it is of benefit. The aim of this meta-analysis is to establish oncologic outcomes for upper third tumors when compared with mid and lower rectal tumors.

Materials and Methods

Literature Search and Study Selection

A systematic search of PubMed and Embase was performed for all studies published relating to tumor characteristics and oncologic outcomes in upper rectal and mid/lower rectal tumors by using the following in the search algorithm: (rectal) AND (upper) AND (surgery) AND (radiation OR neoadjuvant OR radiotherapy). The Cochrane Central Register of Controlled Trials was also searched for articles that investigated tumor characteristics and outcomes for the differing levels of rectal tumors. The latest search was performed on December 21, 2017. Two authors (C.C. and M.F.) independently examined the title and abstract of citations, and the full texts of potentially eligible trials were obtained; disagreements were resolved by discussion. The reference lists of retrieved papers were further screened for additional eligible publications. When data were unclear or incomplete, the corresponding author was contacted to clarify data extraction. Raw data was requested and utilized from original authors where necessary.

Eligibility Criteria

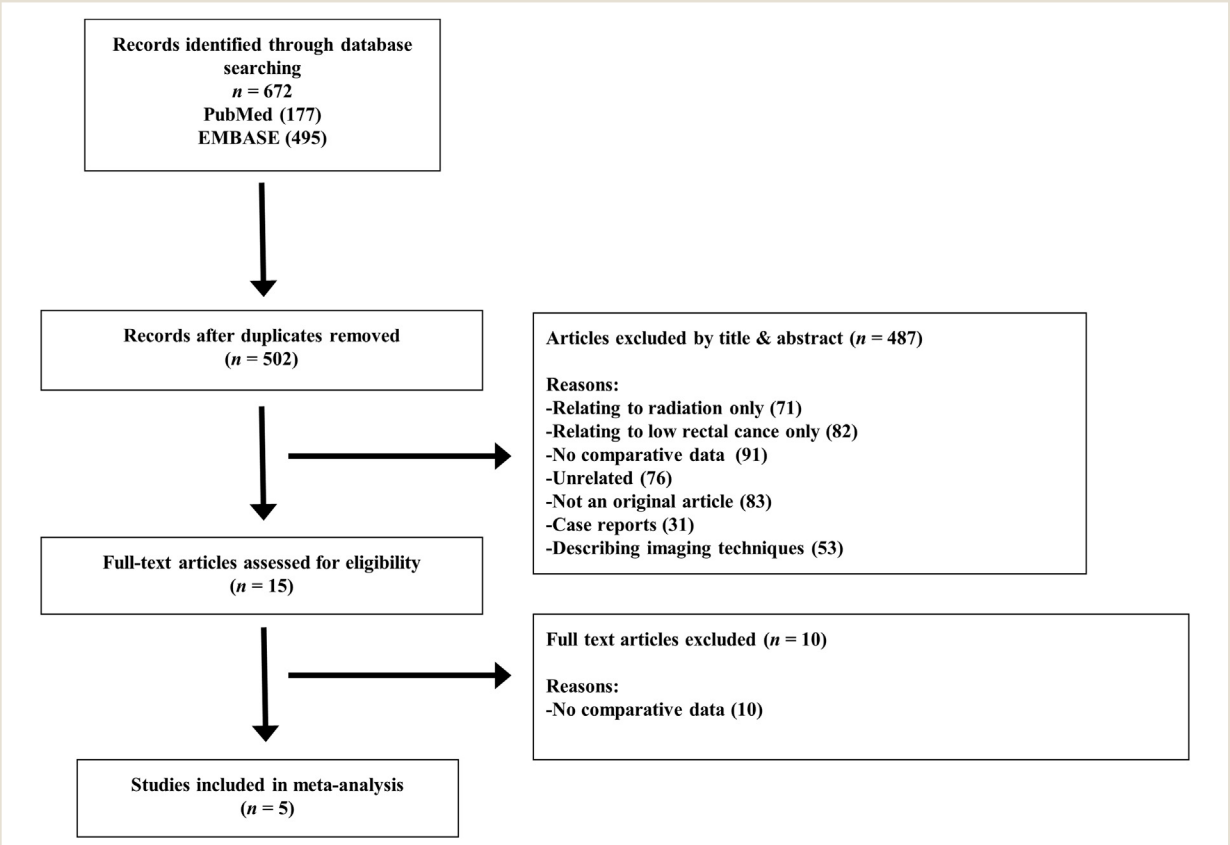
Studies including comparative data on upper third and mid/lower rectal tumors were included for analysis. The primary endpoint of the study was the comparative outcomes of upper rectal tumors treated without neoadjuvant radiation compared with mid/low rectal tumours treated without neoadjuvant radiation. The secondary endpoints included patient demographics, tumor characteristics, and postoperative pathology. Studies that did not define the level of the upper rectum or that defined it above 15 cm were excluded. To ensure homogeneity of data,

Table 1 Characteristics of Included Trials

First Author	Year	Study Type	Enrollment Interval	No. Patients	Sigmoid/Recto-sigmoid Definition, cm	Upper Rectum Definition, cm	Mid/Lower Rectum Definition, cm	Neoadjuvant CRT Mid/Lower Rectal Tumors	Adjuvant Chemotherapy (UR, LR)	Median Follow = up, mos
Park JS[15]	2016	Retrospective	2004-2008	1424	15.1-30	10-15	0-9.9	No	344/660, 292/764	79
Marinello F[16]	2015	Retrospective	1992-2010	456	16-40	11-15	0-10	No	NA	60
Chiang JM[17]	2014	Retrospective	2002-2006	884	NA	10.1-15	0-10	No	NA	78
Rosenberg R[18]	2010	Retrospective	1990-2006	200	15.1-40	10.1-15	0-10	No	42/95, 52/105	80
Bonadeo F[19]	2001	Retrospective	1980-1996	417	NA	11.1-15	0-11	No	NA	62

Abbreviations: CRT = chemoradiotheraphy; LR = mid and lower rectal tumors; NA = not available; Sig = rectosigmoid and sigmoid tumors; UR = upper rectal tumors.

Figure 1 Preferred Reporting Items in Systematic Reviews and Meta-analysis (PRISMA) Diagram



original authors were contacted, and patients who received neoadjuvant treatment in both groups were excluded. There were no language restrictions.

Data Extraction and Outcomes

The following information regarding each eligible trial was recorded: author's names, journal, year of publication, study type, enrollment dates, median follow-up, patient demographics, tumor characteristics, margin positivity, and total number of patients included. Definitions of tumor location by height were recorded for each study. From each eligible study, the disease-free survival and local recurrence rates were recorded.

Statistical Analysis

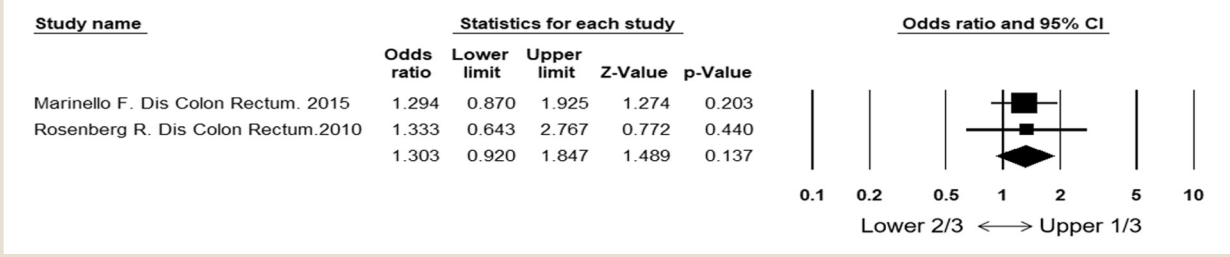
All pooled outcome measures were determined using a random-effects model as described by DerSimonian and Laird,[11] and the odds ratio (OR) was estimated with its variance and 95% confidence interval (CI). The random effects analysis weighted the natural logarithm of each study's OR by the inverse of its variance plus an estimate of the between-study variance in the presence of

Table 2 Comparative Features and Outcomes of Sigmoid, Upper Rectal, and Mid/Lower Rectal Tumors

First Author	No. Patients (UR/LR)	Mean Age, y (UR/LR)	T3/4, % UR/LR	Lymph Node +, % UR/LR	Positive CRM, % UR/LR	5-Year Disease-free Survival, % UR/LR	5-Year Overall Survival, % UR/LR	5-Year Local Recurrence, % UR/LR
Park JS[15]	660/764	65/65	NA	37/35	1.4/1.4	71/62	81/77	3.5/11.1
Marinello F[16]	168/288	67/67	66/60	33/35	15.5/16.9	87/81	NA	4.2/9.0
Chiang JM[17]	436/448	65/67	100/100	55/55	NA	72/56	74/47	8.3/16.3
Rosenberg R[18]	95/105	62/63	84/80	50/59	1/1.4	74/73	NA	15.8/11.4
Bonadeo F[19]	116/301	NA	NA	NA	NA	NA	NA	4.3/9.0

Abbreviations: CRM = circumferential resection margins; LR = mid and lower rectal tumors; NA = not available; UR = upper rectal tumors.

Figure 2 Meta-analysis of T3/4 Tumors in Upper and Mid/Lower Rectal Tumors. Each Study Is Shown by the Point Estimate of the Odds Ratio (OR) (Square Proportional to the Weight of Each Study) and 95% Confidence Interval (CI) for The OR (Extending Lines); the Combined ORs and 95% CIs by Random Effects Calculations Are Shown by Diamonds. T3/4 Tumors and Upper Versus Mid/Lower Location (n = 1540; P = .137; Test for Heterogeneity, Cochran Q: 0.005; df: 1; P = .944; I^2 [Inconsistency] = 0.0)



between-study heterogeneity. As previously described,[12,13] heterogeneity between ORs for the same outcome between different studies was assessed. This was through the use of the I^2 inconsistency test and χ^2-based Cochran Q statistic test,[14] in which $P < .05$ is taken to indicate the presence of significant heterogeneity. Analyses were conducted using Comprehensive Meta-analysis version 2 (Biostat Inc, Englewood, NJ).

Results

Eligible Studies

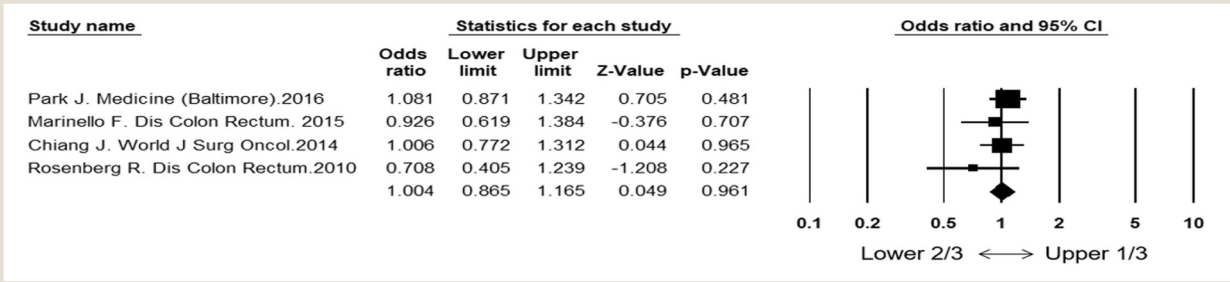
Five published studies containing data comparing upper rectal tumor oncologic outcomes to mid/lower rectal tumors were identified (Table 1).[15-19] The initial search identified 174 articles. Eleven full-text studies were assessed for eligibility, 6 of which were excluded (Figure 1). Two studies defined the upper rectum as 11 to 15 cm[16,19]; the remaining 3 studies defined it as 10 to 15 cm.[15,17,18] There was no significant difference in terms of patient age between upper rectum and mid/lower rectum patients (Table 2). Where reported, more patients with upper rectal tumors received adjuvant chemotherapy compared with those with mid/low rectal tumors (51% and 40%, respectively) (Table 1).[15,18] All studies were published within the last 20 years, and the spectrum of patients was reflective of modern clinical practice. Overall, a total of 3381 patients were included in the final analysis.

Tumor Characteristics

T Stage. Three studies describing 1540 patients included assessable data on T stage (pathologic) and tumor location (Table 2).[16-18] One of the studies included only patients with T3/4 disease, thus it is not included in the meta-analysis (Table 2).[17] There was no statistically significant difference in the proportion of T3/4 tumors between upper location and mid/lower location groups, although a higher frequency of T3/4 tumors in the upper third rectal group approached significance (OR, 1.303; 95% CI, 0.920-1.847; P = .137) (Figure 2).

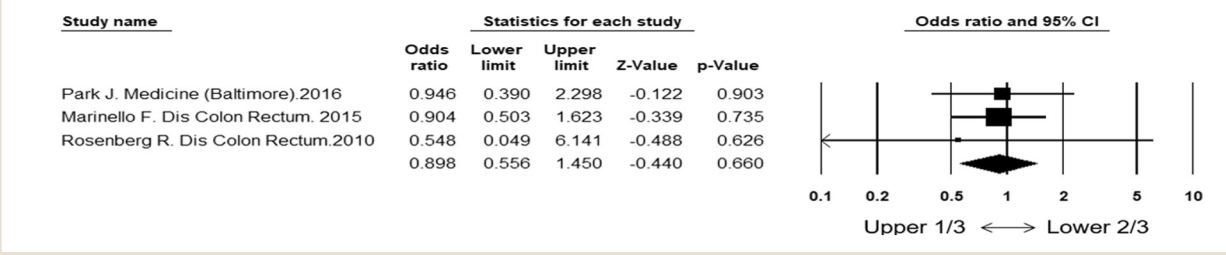
Lymph Node Positivity. Four studies with a total of 2964 patients included data on lymph node positivity and tumor location (Table 2).[15-18] There was no difference in lymph node positivity

Figure 3 Meta-analysis of Lymph Node Positivity in Upper and Mid/Lower Rectal Tumors. Each Study Is Shown by the Point Estimate of the Odds Ratio (OR) (Square Proportional to the Weight of Each Study) and 95% Confidence Interval (CI) for The OR (Extending Lines); the Combined ORs and 95% CIs by Random Effects Calculations Are Shown by Diamonds. Lymph Node Positivity and Upper Versus Mid/Lower Location (n = 2964; P = .961; Test for Heterogeneity Cochran Q: 2.098; df: 3; P = .552, I^2 = 0.0)



Abbreviation: CI = confidence interval.

Figure 4 Meta-analysis of Circumferential Resection Margin Involvement in Upper and Mid/Lower Rectal Tumors. Each Study Is Shown by the Point Estimate of the Odds Ratio (OR) (Square Proportional to the Weight of Each Study) and 95% Confidence Interval (CI) for The OR (Extending Lines); the Combined ORs and 95% CIs by Random Effects Calculations Are Shown by Diamonds. Circumferential Resection Margin Involvement and Upper Versus Mid/Lower Location (n = 1990; P = .660; Test for Heterogeneity Cochran Q: 0.174; df: 2; P = .916; I^2 = 0.0)



Abbreviation: CI = confidence interval.

between upper third and mid/lower rectal cancers (OR, 1.004; 95% CI, 0.865-1.165; P = .961) (Figure 3).

Oncologic Outcomes

Positive Resection Margins. Three studies describing a total of 1990 patients included data on tumor locations and positive circumferential margins (Table 2).[15,16,18] There was no association between rectal tumor location and positive CRMs (OR, 0.898; 95% CI, 0.556-1.450; P = .660) (Figure 4).

Five-year Disease-free and Overall Survival. Four studies describing 2964 patients included data on disease-free survival and tumor location (Table 2).[15-19] There is a decreased risk of distant recurrence with upper third compared with mid/lower rectal tumors (OR, 0.613; 95% CI, 0.511-0.734; P < .001) (Figure 5).

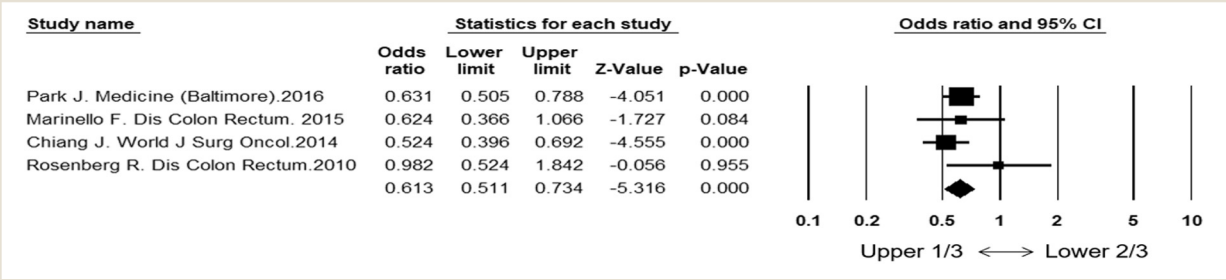
Two studies assessed overall survival relative to tumor location.[15,17] Park et al found that the Kaplan-Meier overall survival curve of patients with upper rectal tumors lay between that of those with sigmoid tumors and those with mid to lower rectal tumors. The 5-year overall survival rates for sigmoid colon, upper rectal, and mid/lower rectum were 88.8%, 81.1%, and 77.1%, respectively.[15] Chiang et al reported significantly worse overall survival for patients with tumors of the low and mid rectum compared with those with upper rectum tumors, with a 5-year overall survival of 47.25% for low rectal tumors and 73.91% for upper rectal tumors.[17]

Local Recurrence. Five studies describing 3381 patients included data on local recurrence and tumor location(Table 2).[15-19] There was a decreased risk of local recurrence with upper third compared with mid/lower rectal tumors (OR, 0.495; 95% CI, 0.302-0.811; P = .005) (Figure 6).[15-19]

Discussion

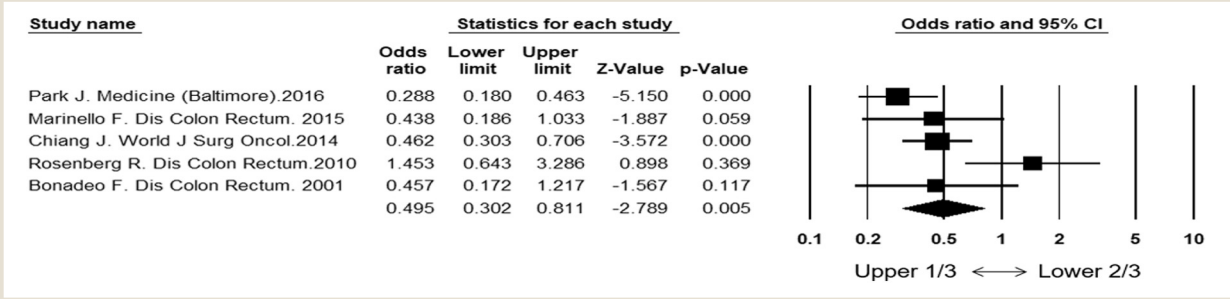
Cancers located in the upper third of the rectum treated with primary resection without the addition of neoadjuvant radiation have lower local and distant recurrence rates compared with cancers located in the mid and lower rectum. There is no difference in the

Figure 5 Meta-analysis of 5-year Disease-free Survival in Upper and Mid/Lower Rectal Tumours. Each Study Is Shown by the Point Estimate of the Odds Ratio (OR) (Square Proportional to the Weight of Each Study) and 95% Confidence Interval (CI) for The OR (Extending Lines); the Combined ORs and 95% CIs by Random Effects Calculations Are Shown by Diamonds. Distant Recurrence in Upper Versus Mid/Lower Location (A = Upper; B = Mid/Lower) (n = 2964; P < .001; Test for Heterogeneity Cochran Q: 3.5; df: 3; P = .327; I^2 = 13.1)



Abbreviation: CI = confidence interval.

Figure 6 Meta-analysis of 5 Year Local Recurrence Rates in Upper and Mid/Lower Rectal Tumors. Each Study Is Shown by the Point Estimate of the Odds Ratio (OR) (Square Proportional to the Weight of Each Study) and 95% Confidence Interval (CI) for The OR (Extending Lines); the Combined ORs and 95% CIs by Random Effects Calculations Are Shown by Diamonds. Local Recurrence in Upper Versus Mid/Lower Location (A = Upper; B = Mid/Lower) (n = 3381; P = .005; Test for Heterogeneity Cochran Q: 11.3; df: 4; P = .023; I^2 = 64.7)



numbers of T3/4 tumors, lymph node positivity, or positive CRMs between upper third and mid/lower tumors.

Conflicting evidence exists regarding the use of neoadjuvant radiation based on several large RCTs and their long-term outcomes. The Dutch TME trial initially found that there was no significant difference in local recurrence or survival between irradiated and non-irradiated patients with upper third rectal tumors at 6-year follow-up.[5] The more recently published 12-year follow-up of the TME trial suggests significant reduction of local recurrence is conferred to all patients regardless of rectal tumor location.[1] The Swedish Rectal Cancer Trial found that neoadjuvant radiation did not significantly reduce local recurrence rates for tumors located above 10 cm from the anal verge at a median follow-up of 13 years.[2] The Stockholm II trial subgroup analysis concluded that omission of neoadjuvant radiation for tumors of the upper rectum was not recommended based on available evidence at that time.[3] Any assessment of oncologic outcomes for upper rectal tumors receiving neoadjuvant radiation must also be considered in the context of radiation side effects and a risk-benefit ratio. To date, there is no study looking specifically at upper rectal tumors with and without radiation and establishing oncologic benefits with associated side effects.

In the absence of randomized studies, multi-disciplinary decision-making may be guided by establishing oncologic benefits associated with tumors in the upper third location in comparison with lower rectal tumors. In this study, where no neoadjuvant treatment was given to upper third tumors, factors such as tumor T stage, lymph node positivity, and, most importantly, the positive resection margin rate were all similar in upper and lower rectal tumors. There was no significant heterogeneity evident for these factors between studies, suggesting that upper third tumors have better prognostic features compared with mid/lower tumors of similar stage with clear margins. All studies described performing a total or partial mesorectal excision (in the case of upper third tumors) and margin positivity was not significantly different, so surgical factors cannot account for the observed difference. An argument may be made that some of the included studies did not treat some mid and lower rectal tumors with neoadjuvant radiation, which is now standard, but the comparison of oncologic outcomes with upper rectal tumors treated without neoadjuvant therapy is key. Two of the studies are from an Asian population in which neoadjuvant chemoradiation was used very selectively for mid/low rectal tumors during the inclusion period.[15,17] Although no longer standard practice, this provides unique insight into this patient group and demonstrates tumor biology that could not be shown in current studies. The remaining studies included middle third tumors that were not deemed to be staged T3 or greater preoperatively and thus went straight to surgery.[16,18,19] Interestingly, several included studies found upper third rectal tumors display greater similarity to sigmoid tumors compared with mid and lower rectal tumors. Marinello et al found no difference in local recurrence, cancer-specific survival, or disease-free survival between sigmoid and upper third rectal tumors.[16] Similarly, Fazio et al found the outcome of upper rectal cancers of whom only 7.9% were treated with neoadjuvant radiation was similar to sigmoid cancers and differed favorably from lower rectal cancers.[20] Conversely, Rosenburg et al found that rectal cancers of the upper third treated without neoadjuvant radiation had no difference in local recurrence but worse cancer-specific survival compared with sigmoid tumors.[18]

The central decision point regarding the use of neoadjuvant radiotherapy for upper rectal tumors lies in the risk-benefit assessment of the marginal improvement of oncologic outcomes versus the significant side effects associated with neoadjuvant treatment. Unfortunately, this data does not exist. This study represents the largest assessment of upper third rectal cancers treated without neoadjuvant radiation in comparison to lower rectal cancers, and findings suggest favorable outcomes for upper third tumors. This is in agreement with current ESMO guidelines regarding the selective use of neoadjuvant chemoradiotherapy in locally advanced T4 upper rectal tumors. An ideal study to establish the benefits of neoadjuvant treatment in upper third rectal cancer would require randomization of upper rectal cancers to neoadjuvant versus no neoadjuvant treatment combined with appropriate surgery and a long-term follow-up to establish oncologic outcomes and radiation-related morbidity.

There are several limitations to our study. All studies included in this meta-analysis are retrospective in nature. Heterogeneity is seen in the results regarding local recurrence. Adjuvant chemotherapy

treatment rates were not fully reported in all studies and could have a significant influence on disease-free survival. Enrollment intervals span a significant time period in which TME techniques have become more refined, neoadjuvant radiation use has become more common, and adjuvant treatments have further evolved. Despite limitations, this study describes a large international dataset and shows patients with upper rectal tumors treated without neoadjuvant radiation have better outcomes compared with those with lower rectal tumors. Further studies to determine the degree of benefit from neoadjuvant treatment and the complications associated with it are required.

Clinical Practice Points

- Randomized studies to date have established the benefit of neoadjuvant radiation in locally advanced rectal cancer but have not analyzed outcomes in distinct anatomical areas of the rectum.
- This meta-analysis examines comparative oncologic outcomes in upper rectal and middle/lower rectal tumors treated with resection without neoadjuvant radiation and demonstrates a marked difference between the 2 groups despite similar TNM stage and margin status.
- These results demonstrate the significant variation in recurrence between the anatomically distinct areas in the rectum when T stage, nodal disease, and surgical factors are accounted for. Further studies examining effects of neoadjuvant radiation in rectal cancer should consider upper rectal tumors as a distinct entity to middle and lower rectal tumors.

Disclosure

The authors have stated that they have no conflicts of interest.

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