Preoperative Radiation Therapy for Upper Rectal Cancer T3, T4/Nx: Selectivity Essential

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Abstract

This review explores the current available literature regarding the role of neoadjuvant therapy for upper locally advanced rectal cancers (≥10 cm-15 cm). Although there is a paucity of data evaluating the outcomes of preoperative chemoradiation for upper rectal cancers, the authors suggest that T3N0 tumors will not likely benefit from radiation and that treatment of T4N0 should be individualized.

Clinical Colorectal Cancer, Vol. xx, No. x, xxx © 2011 Published by Elsevier Inc.

Keywords: Neoadjuvant therapy, Rectal cancer, T3, T4Nx

Introduction

The past two decades have seen major advances in surgical treatment and combined modality therapy of patients who have rectal cancer. For patients who have mid and lower rectal cancer (≤10 to 12 cm) the standard of surgical care now includes total mesorectal excision (TME), which has been shown to significantly decrease local recurrence rates.1 Locoregional recurrence is further reduced with the combination of optimal surgery and chemoradiation therapy. Clinical trials now support the use of preoperative (neoadjuvant) sequencing as the preferred strategy for transmural and/or clinical node positive tumors. It remains controversial as to the selective application of this paradigm when the cancer is above the peritoneal reflection.2 In the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, upper rectal tumors are defined as partially peritonealized, versus tumors of the mid and lower rectum, which are not peritonealized (Figure 1). The significance of this difference translates into a different T stage for transmural upper and lower rectal tumors. For example, for a mid-low rectum, a transmural tumor is always a T3 lesion, whereas a transmural upper rectal tumor is classified as a T4 lesion when located anteriorly, but as a T3 lesion when located posteriorly (Figure 1). Anterior T4 lesions, node negative, frequently receive adjuvant postoperative chemotherapy only. Patients with T3N0 lesions have a better prognosis compared to patients with other types of locally advanced rectal cancer, as reflected by the modifications made in the 7th edition of the AJCC cancer staging manual.

It has been well-demonstrated that neoadjuvant radiotherapy (RT) improves local recurrence rates in locally advanced rectal cancer for which the circumferential radial margin (CRM) is the most important prognostic marker of recurrence.2-4 For upper rectal tumors located above the peritoneal reflection (≥10 to 12 cm), one could argue that circumferential margin is free from the anatomically restrictive pelvis and clear radial margins more feasible to obtain. In addition, it remains unclear if neoadjuvant RT has the same efficacy and results with upper rectal lesions. Although, when cancer-specific survival was examined, upper rectal cancers behaved more like mid and lower rectal than sigmoid cancers. Local recurrence was not investigated.5

This review article examines the current available literature concerning the treatment paradigms and treatment outcomes for T3T4 Nx upper rectal cancers.

In the last decade, neoadjuvant RT has emerged as the preeminent mode of treatment for locally advanced rectal cancer in terms of local recurrence rates and toxicity. In 2004, the German Rectal Cancer Study Group compared local recurrence and overall survival rates for rectal cancer patients treated with neoadjuvant versus adjuvant chemoradiation therapy (CMT) and found significantly improved rates of local recurrence in the neoadjuvant arm (6% versus 13%, P = .006), yet no difference in overall survival.6 A few years later, the MRC CR07/NCIC CTG C0167 study confirmed the superiority of neoadjuvant RT compared to selective adjuvant RT, the latter of which delivered radiation only in patients with close circumferential margin. This study demonstrated a 61% relative risk reduction in local recurrence in the neoadjuvant arm (P < .0001). A second critical benefit of neoadjuvant RT is the decrease in rates of acute and chronic toxicity,
translating into more patients completing treatment with less postoperative anorectal dysfunction.8-11

**Imaging for Staging of Rectal Cancer**

The assumption behind asking the question, “Do upper rectal cancer patients benefit from neoadjuvant radiotherapy?” is that these patients can be accurately identified preoperatively. In fact, one of the main obstacles in answering this question is the ambiguity of preoperative clinical staging. Currently, in the United States, preoperative staging consists of a combination of imaging modalities including computed tomography (CT), endorectal ultrasound (ERUS), and magnetic resonance imaging (MRI). The decision of which modality to pursue is often based on local expertise and availability. In contrast, in Europe, preoperative staging uses high-resolution MRI to estimate the CRM. Whereas in the United States, currently all T3N0 patients are offered neoadjuvant CMT and adjuvant chemotherapy. In Europe, the estimated CRM determines which patients will receive neoadjuvant RT.12

The Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study (MERCURY) trial, published in 2006, set the standard for preoperative assessment of CRM with a specificity of 92% using high-resolution MRI.13 In this trial, the authors used high-resolution MRI to estimate the CRM in 408 consecutive rectal cancer patients. These estimates were then contrasted to the actual pathologic findings. Although distance from the anal verge is one of the variables studied, the authors do not discuss variation in accuracy based on tumor location. One important limitation discussed is the inaccuracy of lymph node identification. MRI is able to identify lymph nodes greater than 1 cm in size. However, although suggestive, size is not pathognomonic of malignancy. Several smaller studies have evaluated and compared the efficacy of CT scanning to MRI with mixed results. Studies have shown that multidetector-row CT14 has a poor accuracy rate in evaluating CRM in low rectal cancers and moderate accuracy in mid to high rectal cancers, but is not superior to MRI.14,15

ERUS was first used to stage rectal cancer in 1985,15 and use of this modality has increased. ERUS has established itself as a key component of preoperative staging for rectal cancer,16 however, exactly where in the paradigm of preoperative imaging it lies has yet to be refined. A small study published in 200817 comparing ERUS and MRI in preoperative staging for rectal cancer found that accuracy of T staging was slightly higher with MRI than ERUS (85% versus 89%), whereas both modalities had poor identification of lymph node involvement (76% versus 74%). A recent meta-analysis evaluating the sensitivity of ERUS for identification of lymph node involvement in 2732 patients demonstrated a pooled sensitivity of 73.2% (95% confidence interval [95% CI] 70.6-75.6) and specificity of 75.8% (95% CI 73.5-78).18 Enthusiasm for ERUS has waned recently, reflecting the recent trend toward lower rates of accuracy published in the literature, which has prompted concerns about publication bias19,20 or increased use by inexperienced physicians.19

There has been suggestion that the addition of fine-needle aspiration to ERUS would add a significant diagnostic benefit, however, the data so far has not borne this out.21

A meta-analysis from the Netherlands22 compared the sensitivity and specificity of all three imaging techniques (ERUS, CT, and MRI) in preoperative staging for rectal cancer. ERUS and MRI had comparable sensitivity in estimating invasion of the muscularis propria (94%, 95% CI 90-97 versus 94%, 95% CI 89-97), but ERUS was significantly more specific than MRI (86%, 95% CI 80-90 versus 69%, 95% CI 52-82, P = .02). No data was available for CT. In assessing perirectal tissue invasion, ERUS was significantly more sensitive than either CT or MRI (90%, 95% CI 88-92 versus 79%, 95% CI 74-84, versus 82%, 95% CI 74-87, P = .003), although the specificities were similar (75%, 95% CI 69-81 versus 78%, 95% CI 73-83 versus 76%, 95% CI 65-84). Lastly, there was no significant difference found between the three modalities in diagnosing adjacent organ or lymph node involvement. The authors conclude that ERUS is the most accurate modality for preoperative staging of locally advanced rectal cancer, however, they note the continued inaccuracy of identification of lymph node involvement is a significant limitation of all three imaging modalities. Upper rectal tumors are even more difficult to study and accurately differentiate between a T3 and T4 Nx lesion with a rigid ERUS. Currently ERUS and MRI are the standard modalities used in the United States for staging of rectal cancer.

**Local Recurrence**

There are three major trials evaluating local recurrence in rectal cancer with neoadjuvant and adjuvant therapy that include data based on tumor location (Table 1). The first trial, the Swedish Rectal Cancer Trial23 published in 1997, was a landmark article demonstrating significant improvements in local control and overall survival for patients undergoing neoadjuvant short-course RT. The study population was composed of stage I to III patients diagnosed using
barium enema and rigid proctoscope, 27% of whom had upper rectal lesions (> 11 cm from anal verge). The authors found that neoadjuvant treatment with short-course RT had a significant effect on decreasing rates of local recurrence for mid and low rectal tumors ($P < .001, P = .003$), however, the effect on upper rectal tumors was not significant ($P = .3$) on long-term follow-up.24

The Dutch TME trial,25 the first trial to standardize surgical therapy, also found a significant correlation between local recurrence rates and tumor location within the rectum. Of the 1805 patients included in the trial, 30% had upper rectal tumors (10.1 to 15 cm from anal verge), 40% were mid-rectal (5.1 to 10 cm), and 30% were lower rectal (< 5 cm) tumors as determined by flexible endoscopy. The patient population was also included all stages of disease, the majority of whom were stage I-III. The data at 2-year follow-up shows that both mid-rectal tumors and lower rectal tumors had a significantly higher risk of developing local recurrence compared to upper rectal tumors (hazard ratio [HR] $2.13, 95\%$ CI $1.13-4.0$, $P = .02$; HR $2.78, 95\%$ CI $1.22-6.31$, $P = .02$). However, on univariate subgroup analysis, patients with upper rectal tumors who were administered neoadjuvant RT were found to have no improvement in local recurrence rates ($P = .17$) compared to the surgery-alone cohort at 2-year follow-up; these results were confirmed at 5-year follow-up ($P = .122$).26

The third trial, the German CAO/ARO/AIO trial,6 is limited to patients with T3/4 tumors who were staged with ERUS and CT scans, 15% of whom had upper rectal lesions (> 10 cm from anal verge). The authors do not include the data from their subset analysis, only the conclusion that there was no difference in local recurrence outcomes between upper and lower rectal tumors.27

None of the aforementioned trials were designed or powered to evaluate the benefit of radiation in the subset of patients with T3/4N0 disease. Nonetheless, the Swedish and Dutch studies suggest that the absolute benefit of RT in this subset is, if present, a small one. Gunderson et al28 combined data from five randomized studies to examine the relationship between survival and relapse and T and N stage, as well as treatment modalities. They evaluated data from a total of 3791 patients and used these data to create a risk classification comprised of four categories (low, intermediate, moderately high, high) based on local recurrence and survival rates. Higher T stage lesions are categorized as intermediate-risk based on the overall 5-year survival rate of 75% and local recurrence rate of 9%. The authors note that patients in subgroups who received neoadjuvant RT had lower recurrence rates (5% to 10%) compared to patients who were treated with surgery alone (11%). Unfortunately, they did not have data concerning tumor location within the rectum; therefore, although the authors extrapolate that trimodality treatment of intermediate-risk tumors may be excessive and unnecessary, no definitive recommendations can be made at this juncture. Several smaller studies concerning patients with only T3N0 rectal cancer treated with surgery alone have reported 5-year local recurrence, systemic recurrence, and survival rates comparable to cohorts of patients treated with neoadjuvant or adjuvant CMT.29-31 However, these studies do not differentiate tumor location within the rectum and have small patient populations, therefore suggesting the further need into investigating if and when it is safe to treat T3N0 patients with surgery alone.

### Predictors of Local Recurrence

It has been well-established that CRM has important prognostic value concerning local and distal recurrence in rectal cancer. What has not been well-established is the relevance of CRM in upper rectal cancer. In contrast to low and middle tumors constrained by a narrow pelvis, upper rectal tumors are not bound by similar physical limitations. Thus, it has been hypothesized that CRM has less importance as a prognostic indicator in upper rectal tumors. One study2 comparing the 5-year local and systemic recurrence rates between patients with positive CRM ($n = 460$) and patients with negative CRM ($n = 44$) found that 5-year local recurrence was 35% in patients with a positive CRM compared to 11% in the negative-CRM group ($P = .010$); 5-year systemic recurrence was 60% in the positive-CRM and 25% in the negative-CRM group ($P < .001$). Upper rectal tumors comprised 24% of the negative-CRM group and 23% of the positive-CRM group; however, there was no significant correlation between tumor location and rate of CRM positivity or negativity ($P = .466$). Bernstein et al3 also studied the predictive impact of CRM after surgery to identify the ideal CRM. The authors looked at a much larger study group ($n = 3196$) than the aforementioned study and found that patients with CRM of 0 to 2 mm had a local recurrence of 23.7% compared to 8.9% in patients with wider mas-

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<th>Table 1</th>
<th>Local Recurrence in Rectal Cancer With Neoadjuvant and Adjuvant Therapy</th>
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<td><strong>Trial</strong> (Year Results Published)</td>
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<td><strong>German Rectal Cancer Study Group (2004)</strong></td>
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*Abbreviations: MSKCC = Memorial Sloan-Kettering Cancer Center; RCT = randomized controlled trial; RT = radiation therapy; TME = total mesorectal excision.*
Preoperative RT for Upper Rectal Cancer

Margins. Overall survival was 44.5% in the CRM 0-2-mm group and 66.7% in patients with wider margins. In the setting of TME surgery without RT, the authors found that patients with mid-rectal tumors are 38% more likely to have local recurrence than upper rectal tumors, and low rectal tumors are 72% more likely to have a local recurrence (HR 1.38, CI 1.01, 1.89; HR 1.72, CI 1.06, 2.79; P = .047). They also found a significant correlation between local recurrence and CRM status in upper rectal lesions. They report that a CRM of 0 to 2 mm nearly doubles the risk of having a local recurrence compared to CRM > 3 mm (HR 1.97, 95% CI 1.03, 3.77, P = .044), suggesting that CRM is relevant in upper rectal tumors. To conclude, CRM margins and, in particular, CRM margins more than 2 mm, are critical for all heights of rectal tumors. The MRC CR07 trial attempted to determine if RT could be delivered selectively to only those patients with close CRM by randomizing patients to neoadjuvant RT versus adjuvant RT only if CRM was < 1 mm. Approximately 12% of patients in the selective adjuvant radiation arm had close margins and received RT. Local recurrence rates were decreased with neoadjuvant RT compared to selective adjuvant RT. Although this study suggests that local recurrences are lowest with preoperative radiation, it raises the question of whether clinical predictors of CRM margins, such as an MRI scan, could allow physicians to be able to more intelligently select patients requiring preoperative therapy.

Another approach to the question of which higher T stage patients benefit from neoadjuvant RT is to evaluate predictors of recurrence. In a series of 100 consecutive pT2/T3 N0 patients studied over a period of 6.5 years, lymphovascular invasion, preoperative carcinoembryonic antigen levels > 5 ng/mL, and patients older than 70 years were factors predictive of poor outcome. The authors of this study did not include data concerning tumor location within the rectum, however, they report local and distal recurrence rates of 4.1% and 28.6%, respectively, for locally advanced tumors treated with surgery alone. The authors state that treatment for uT3N0 rectal cancer is radical surgery with TME and postulate that preoperative identification of high-risk patients allows refinement of the population of T3N0 patients who receive neoadjuvant RT to those who truly benefit from it. A study published in 2008 designed to address the questions surrounding optimal management of T3N0 tumors regardless of tumor height further obfuscates the issue. One hundred eighty-eight uT3N0 patients were treated with neoadjuvant CMT followed by surgery. The preoperative stage was compared to the postoperative pathologic stage. Positive lymph nodes were identified in 22% of patients. The incidence of involved lymph nodes corresponded to pathologic T stage (ypT0 3%, ypT1 7%, ypT2 20%, ypT3-4 36%, P = .001); suggesting that significant preoperative understaging of rectal cancer occurs in at least 22% of patients. Distance from the anal verge was included as a tumor variable and the incidence of lymph node positivity was not related to distance from the anal verge (P = .58). The authors conclude that the risk of overtreatment is lower than the risk of undertreatment and recommend that locally aggressive tumors (T3 N0), independent of height from the anal verge, should be treated with neoadjuvant CMT. Conversely, we could argue that if the pathologic examination has shown that the upper rectal tumor with adequate CRM was significantly understaged, or that surgery alone was not optimal, those patients could receive adjuvant therapy. The potential drawback to this approach is a small decrease in local control with adjuvant versus neoadjuvant RT and increase in toxicity as demonstrated in the German Rectal Cancer Study Group.

Summary

There is a paucity of data evaluating the outcomes of locally advanced upper rectal cancer treated with and without neoadjuvant RT. Although several surrogate markers have been proposed for use in determining which patients would benefit from neoadjuvant RT, adequate CRM is the only variable shown in large population studies to correlate with local recurrence rates in upper rectal cancer. Synthesizing the available data suggests that a subset of upper locally advanced rectal cancers will not experience local recurrence, and in this subset of patients, neoadjuvant RT only increases toxicity rates, both acute and chronic.

Accurate preoperative staging is key to making informed decisions regarding patient treatment because adjuvant CMT is less effective and more toxic than neoadjuvant CMT. Careful physical examination combined with rigid proctoscopy can facilitate defining the clinical location. Looking at the CT scan from the perspective of tumor location provides additional relevant information, such as, is the patient male or female? And, if the latter, did she have a prior hysterectomy? Because of the risk of local recurrence and the associated diminution of quality of life, the importance of appropriately and selectively treating locally advanced rectal cancer with neoadjuvant therapy intensifies. We propose that most patients with T3N0 upper rectal tumors will not benefit from RT, and future randomized trials should be considered in this subgroup of patients. Treatment of T4N0 should be individualized. RT is likely of limited benefit for patients with T4 disease by virtue of anterior extension through the peritoneal surface, and these patients may be considered for adjuvant single-modality chemotherapy. Extensive nodal metastases or adherence of a transmural tumor to the pelvic sidewall may be an indication for postoperative chemoradiation. Local recurrence genetic signatures, independent of tumor distance from the anal verge, may represent the next major breakthrough in the management paradigm of locally advanced rectal cancer.

References