Where Should Radiotherapy Stand in the Current era of Rectal Cancer Management?

Duygu SEZEN,¹ Nüliefer KILIÇ DURANKUŞ,¹ Yasemin BÖLÜKBAŞ,¹,2,3 Uğur SELEK¹,2,3

¹Department of Radiation Oncology, Koç University, School of Medicine, Istanbul-Turkey
²Department of Radiation Oncology, American Hospital, UT MD Anderson Radiation Treatment Center, Istanbul-Turkey
³Department of Radiation Oncology, Hospital/University of Texas M.D. Anderson Cancer Center, Houston,TX-ABD

SUMMARY
Rectal cancer management can be defined as maximizing local tumor control and overall survival while preserving anal sphincter, bladder, and sexual functions or improving the quality of life with an overall reduction in morbidity. Appropriate preoperative or postoperative therapy is required to minimize the risks of both local and distant recurrence. Preoperative radiotherapy is the current standard for treating patients with high-risk rectal cancer owing to lower rates of local relapse and toxicity. Modern radiotherapy capabilities are well suited for any short- or long-course protocol with decreased toxicity in irradiated structures such as the small intestine, bladder, or femoral heads. As clinicians and researchers, we must aim to establish tailored treatments for these patients based on the most suitable evidence based on a multidisciplinary environment regarding the expectations of both our patients and team physicians. Herein, we present a review of ongoing clinical trials in order to shed light on the current debates of standard approaches for treating rectal cancer.

Keywords: Long course, neoadjuvant; non-operative management; preoperative; rectal cancer; short course; total neoadjuvant.

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Introduction
Rectal cancer management can be simply defined as maximizing local tumor control and overall survival while preserving anal sphincter, bladder, and sexual functions or improving the quality of life with an overall reduction in morbidity.

It is well known that different risks of both local and distant recurrence mandate a tailored approach, including appropriate preoperative or postoperative therapy; therefore, all subsequent modalities and their timings must be optimized according to prognostic evaluation. The prognosis of patients with rectal cancer is determined mostly based on defined factors.

The most important prognostic criteria are provided by histopathology. TNM staging is independent prognostic factor according to multivariate analysis, whereas size, differentiation, and vascular invasion are independent prognostic factors according to univariate analysis. The following parameters should be assessed when initially deciding the local recurrence risk: T stage with depth of extramural spread in mm, N stage with lymph node involvement, extramural vascular invasion, circumferential resection margin status, and peritoneal perforation caused by the tumor. Tumor stage T3 increases local recurrence risk, thereby resulting in prognostic inhomogeneity. Patients with T3 tumors have been demonstrated to have a significantly longer cancer-specific survival if extramural invasion is less than 5 mm in pathology (5-year survival rate: 85% vs. 54%),[1] The risk propagates with increasing tumor invasion into the perirectal fat to increase nodal involvement.[2] Lymph node involvement has long been identified as an independent adverse prognostic factor.[3] The extent of nodal involvement with four or more tumor-positive nodes has started to be more relevant for pelvic recurrence after total mesorectal excision (TME) in comparison to any nodal involvement predicting recurrence before TME.[4]

The involvement of circumferential resection margin (CRM) is also an independent prognostic factor,[2] and its significance for local recurrence, distant metastases, and survival persists despite TME.[5,6] TME is the current standard of surgery as the middle and lower rectum are resected together with the mesorectum,[7-9] and this surgical approach is said to decrease local recurrence,[7-12] along with a decrease in positive CRM. Therefore, patients with potential for CRM positivity should be given neoadjuvant treatment to decrease related risks. The incidence of positive circumferential radial margins in a Polish study was found to be lower after long-course chemoradiotherapy in comparison to short-course radiotherapy (4% vs 13%, P=0.017).[13] If the final pathology defines an involved CRM, postoperative treatment unfortunately appears to have a limited ability to compensate, as reported in a subset analysis of the Dutch CKVO trial, which demonstrated the inefficacy of postoperative long-course radiation alone to decrease local recurrences,[14] and in the MRC CR-07 trial, which revealed a local recurrence rate of 11% despite postoperative long-course chemoradiotherapy.[15]

Evolution of Preoperative Radiotherapy
We have shed light on the discussion of preoperative versus postoperative radiotherapy first with two phase 3 trials defining decreasing local recurrence and complication rates with preoperative radiotherapy.[16,17] A Swedish trial of 5x5 Gy preoperative radiotherapy alone versus 60 Gy postoperative radiotherapyrandomizing 471 patients reported a significant decrease in local recurrence (5-year recurrence: preop 22%, postop 11%)[16] and complication rates related with obstruction (5-year: preop 5%, postop 11%).[16] These results were confirmed 13 years later with a German chemoradiotherapy trial of preoperative (30.4 Gy and 2.74 mg/m²/day 5FU 1st, 5th weeks) versus postoperative (50.4 Gy+5.4 Gy boost and PV1 1 mg/m²/day 5FU 1st, 5th weeks) radiotherapy randomizing 823 patients.[17] This trial delineated the superiority of the preoperative approach with a decrease in local recurrence (5-year recurrence: preop 6%, postop 13%) and acute and late complication rates (acute: preop 27%, postop 40%; late: preop 14%, postop 24%). The overall survival did not differ in both trials.

The utility of radiotherapy in rectal cancers was questioned via two important meta-analyses, and its robust role has been verified.[18,19] The Colorectal Cancer Collaborative Group evaluated 22 trials, including 8500 cases, and concluded that both preoperative (46% decrement in local recurrence) and postoperative (32% decrement in local recurrence) radiotherapy provides local control benefit over surgery alone.[18] The Swedish Council of Technology Assessment in Health Care reported their analysis of 42 randomized studies, 3 meta-analyses, and 36 prospective and 7 retrospective studies (including 25000 cases) and concluded that preoperative radiotherapy ensures better local control in comparison to postoperative radiotherapy.[19] It should be noted that preoperative single-modality radiotherapy significantly increased overall survival by 10%, whereas postoperative radiotherapy failed to reach significance without chemotherapy.

Sphincter preservation was also an issue to be questioned in preoperative chemoradiotherapy trials. The two randomized trials of conventionally fractionated preoperative versus postoperative chemoradiotherapy for clinically resectable rectal cancer reported contradictory results for sphincter preservation: sphincter preservation significantly increased in the German trial (39% vs 20%, P=0.004) [17]; no significance was reported in the NSABP R-03 trial (48% vs 39%).[20] As the NSABP trial had limitations in statistical power due to low accrual (267 patients of the 900 planned), the German trial delineates the standard for sphincter preservation using preoperative chemoradiotherapy.

Although 18% of patients clinically staged as T3N0 in the German trial who underwent initial surgery without neoadjuvant treatment were found to be pathologically T1-2N0 with overtreatment debates, the Memorial Sloan-Kettering Cancer Center data revealed that 22% of clinically staged T3N0 patients who completed neoadjuvant chemoradiotherapy were proved to be ypN+.[21]

Short Course versus Long Course
Preoperative radiotherapy has been shown to be preferable to postoperative radiotherapy with lower rates of local relapse and toxicity.[16,17] The regimens dif-
adjuvant radiotherapy has been developed to offer long-course in Southern Europe and America. Neo-fer in the preoperative radiotherapy approach, where studies of the Dutch TME trial [14,29] and Medical at 13 years.[28] Even in the TME era, randomized result in an absolute overall survival benefit of 8%.

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The Rotterdam and EORTC trials evaluated 34.5 Gy in 21 fractions concomitant chemoradiotherapy and revealed local control benefit besides subgroup overall survival benefit for patients with T3-4 tumors resected curatively.[22,23] The Swedish trial was the first randomised study demonstrating overall survival benefit for all cohorts with preoperative radiotherapy.

A total of 1168 patients with clinically resectable rectal cancer were randomised to 25 Gy (5Gy/fraction/day) preoperative radiotherapy and immediate surgery in 1 week versus surgery alone; local tumor control and overall survival benefit was obtained with preoperative radiotherapy. In the TME era, a Dutch trial evaluated the same protocol and indicated a significant decrease in local failures (surgery alone: 8.2% vs. radiotherapy+surgery: 2.4%) and a longer follow-up requirement for survival.[25]

Randomized trials testing short-course neoadjuvant radiotherapy accumulated evidence to be safe and efficient (Stockholm I [26], Stockholm II [27], Swedish trial [28], 5×5 Gy with immediate surgery vs surgery alone; Uppsala, 5×5 Gy with immediate surgery vs postoperative radiotherapy, 60 Gy, 2 Gy per fraction [16]; Dutch TME trial [14,29], MRC CR07 [15], 5×5 Gy with immediate surgery vs surgery alone or postoperative radiotherapy for high-risk patients; Stock- holm III trial [30], 5×5 Gy with immediate surgery as group 1 vs 5×5 Gy with surgery after 4–8 weeks as group 2 vs 25×2 Gy with surgery after 4–8 weeks as group 3). The Stockholm III trial recently concluded that short-course radiotherapy with delay in surgery appeared to be a convenient alternative to conventional short-course radiotherapy with immediate surgery.[31]

Swedish trials [26-28] comparing surgery alone with neoadjuvant short-course radiotherapy and immediate surgery identified that radiotherapy reduced local recurrence ranging from 52% to 65% as well as resulted in an absolute overall survival benefit of 8% at 13 years.[28] Even in the TME era, randomized studies of the Dutch TME trial [14,29] and Medical Research Council (MRC) CR07 trial [15] showed an approximately 50%–60% relative reduction of local recurrence after short-course preoperative radiotherapy with an absolute local control benefit of 5%–6%, whereas no overall survival benefit with radiation was found this time.

The literature was lacking randomized trials comparing neoadjuvant short-course radiotherapy with neoadjuvant chemoradiotherapy for T3 cancers until the results of two trials questioning this dilemma: [13 32-35] a Polish study, which evaluated differences in the rates of sphincter-preserving surgery between long-course chemoradiation and short-course radiotherapy, and an Australian study, which evaluated differences in local recurrence rates between these arms. Both trials demonstrated significantly increased early radiation toxicity in the chemoradiation group (grade 3–4 acute toxicity rates, Polish: 18% vs. 3%; Australian: 28% vs. 1.9%), which turned into improved adherence to the protocol in short-course radiotherapy only arms. Interestingly, the sphincter-preservation rates were similar in both arms of the Polish trial (short: 61% and long: 58%), whereas the local recurrence rate was lower in the short arm (short: 10.6% and long: 15.6%). Although the follow-up is very short, no significant differences were observed between the randomized groups regarding survival, postoperative complications, late toxicity rates (severe late toxicity, Polish: 10.1% vs. 7.1%; Australian: 7.6% vs. 8.8%), quality of life, and anorectal and sexual functions.

There has been a debate about whether preoperative chemoradiotherapy or short-course radiotherapy is preferable for patients with threatened CRMs and those with low-lying cancer to increase the chance of anterior resection.[14,36] There is a consensus that neoadjuvant chemoradiotherapy is the treatment of choice for unresectable cancers, but the major conflict is for resectable lesions with threatened CRMs.

The recent two trials did not exclude patients with resectable tumors having involved CRMs, and the subgroup analysis of Dutch TME (18.2% of enrolled patients) [14] and MRC CR07 trials (10.8% of enrolled patients) [15] revealed that the local recurrence rates were lower in neoadjuvant short-course radiotherapy arms in comparison to selective postoperative chemoradiotherapy arms (Dutch: 9.3% vs 16.4% and MRC: 13.8% vs 20.7%). Based on this data, short-course preoperative radiotherapy appeared to be more effective than selective conventional radiotherapy or chemoradiotherapy in case of resectable cancer with threatened CRMs in preoperative imaging. Besides, the Polish study [13] as well as the two systematic reviews [37,38] could not discover any improvement with neoadjuvant chemoradiotherapy in terms of sphincter preservation in comparison to neoadjuvant short-course radiotherapy alone despite the hypothesis of better reduction in tumor bulk after chemoradiotherapy for anterior resection to spare sphincter function.

Overall, the combined MRC CR07/NCIC-CTG C016 trial randomized 1350 patients with rectal cancer to preoperative short-course radiotherapy of 25 Gy (5×5 Gy) or selective postoperative chemoradiation of 45 Gy (3×15 Gy) with concurrent FU for patients with an involved CRM.[15,39] Although no overall survival benefit was outlined between the two arms, this study noted 61% reduction in the relative risk of local recurrence with preoperative radiotherapy besides an absolute difference of 6.2% at 3 years (local recurrence with preoperative radiotherapy: 4.4%; postoperative chemoradiotherapy: 10.6%) and 24% improvement in disease-free survival with preoperative radiotherapy besides an absolute difference of 6% at 3 years (77.5% vs 71.5%).[15,39] The importance of achieving a negative CRM was also confirmed with special notification to the trial team: any suspicious CRM is an independent predictor of local recurrence according to multivariate analysis, and involved margins caused a three-fold increased risk of local recurrence (17% vs 6%) and a reduced 3-year disease-free survival (50% vs 79%).[15,39] This study delineated important aspects that affect the adjuvant treatment approach: local recurrence rates are lower in upper-third rectal cancers in comparison to lower-third tumors, and recurrence rates increase with more advanced TNM stage as well as with involvement of CRM. The CR07/C016 trial declared that surgery should be performed correctly, adjuvant radiotherapy should be considered preoperatively, and short-term radiotherapy alone is safe and efficient.

The recent phase III Polish II trial for cT3 rectal cancer investigated the comparison of long-course preoperative chemoradiation of 50.4 Gy in 28 fractions combined with two 5-day cycles of bolus 5-FU (1.5 g/m²) with concurrent 5-FU for patients with an involved CRM.[40] The CR07/C016 trial revealed no difference in the surgical approach from ad- dominoperineal resection to sphincter preservation in 23%–85% (median: 75%), whereas the complete pathological response rates were 9%–19% and local recur- rence rates were 0%–17%.[49-54] The interval to sur- gery for postoperative radiotherapy was 2 weeks versus 6–8 weeks in a Lyon study and the complete surgical response was 10% at 2 weeks and 26% at 6–8 weeks.[42] However, the pathological response increased when surgery was delayed even for short-course 5×5 Gy regimen in unresectable cases.[30,55-56] The appropriate interval after chemoradiation for surgery timing was assessed in multiple retrospective database studies and National Cancer Center Database (NCDB) analyses, and it was found that intervals more than 8 weeks were associated with increased complete pathological response rates without any increase in surgical complications, [57] higher odds of positive margins and plateauing pathological down-staging, [58] increased odds of positive surgical margins in addition to decreased rate of sphincter preservation, and increased risk of death.[59] GREECAR-6 is a multicenter, randomized, controlled trial conducted for patients with rectal cancer to evaluate the effect of interval between neoadjuvant chemoradiation and surgery at 7 versus 11 weeks on complete pathological response; the results of the trial revealed no difference in the complete pathological response rates (15% vs. 17.3%), whereas the 11-week group had worse rate of complete TME and more medical complications.[60]

Selective Use of Radiotherapy

The general hypothesis was to avoid radiotherapy after an objective clinical response in a subset of pa-
patients receiving neoadjuvant chemotherapy. The initial effort was made in a pilot phase 2 MSKCC study enrolling 32 patients [61] who were candidates for low anterior resection with TME and received six cycles of FOLFOX, with bevacizumab included for cycles 1 to 4, and were planned to undergo radiation before TME if stable/progressive disease detected, whereas respondents were to undergo immediate TME; postoperative radiation was administered if R0 resection could not be achieved. All study participants underwent R0 resections, whereas two were withdrawn due to cardiac events during chemotherapy and received preoperative chemoradiation. For this group, no-field-free survival was 84%, which did not seem to compromise outcomes and encouraged neoadjuvant chemotherapy and selective radiation for selected patients with clinically staged II–III rectal cancer. Therefore, a randomized phase III trial named “Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemoradiotherapy and TME (PROSPECT)” is open to validate this experience by comparing 5-fluorouracil or capecitabine and 5.5 weeks of radiation therapy followed by TME and adjuvant therapy of eight cycles of FOLFOX versus completing FOLFOX chemoradiotherapy once every 2 weeks for six cycles over a total of 12 weeks and MRI or endorectal ultrasound response by 20% or more proceeding to TME or by less than 20% receiving SFU chemoradiotherapy then TME completed with adjuvant FOLFOX after surgery.

Total Neoadjuvant Therapy

Neoadjuvant therapy has also been investigated as a total preoperative therapy with upfront rather than adjuvant chemotherapy to further improve outcomes by addressing possible micrometastatic disease as well as the primary tumor. Two phase II studies, UK and Spain trials, have evaluated induction chemotherapy followed by preoperative CRT in high-risk patients based on MRI for assessing the extent of extramural tumor invasion and risk of CRM positivity.[62,63] Induction CAPOX chemotherapy before CRT in the UK EXPERT and Spanish GCR-3 trials had similar PCR and complete resection rates in comparison to postoperative adjuvant CAPOX, whereas more favorable compliance and toxicity profiles were achieved [63,64] Similarly, in the MSKCC study, total neoadjuvant radiotherapy with FOLFOX and chemoradiation followed by planned TME resulted in a considerable rate of pathCR and delivery of planned therapy in addition to offering a very selective decent stand for possible non-operative management.[65] in FOLF0X6 chemotherapy after concur-
60. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a


