Curr Colorectal Cancer Rep (2016) 12:266–273
DOI 10.1007/s11888-016-0333-6

Treatment of High Rectal Cancers: Do We Need Radiation?

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Published online: 30 July 2016

Abstract Before total mesorectal excision (TME) and radiation therapy/chemoradiation therapy (RT/CRT) were widely adopted in the treatment of rectal cancer, surgery alone was the standard. Therapies have since evolved to neoadjuvant RT or CRT followed by TME as the established paradigm for locally advanced disease. More recently, issues of toxicity and systemic metastasis have risen to the forefront, prompting the exploration of individualized strategies in an attempt to maximize potential cure and local control yet minimize late toxicities. In this article, we will focus on the treatment of high rectal cancers, exploring the specific role of pelvic radiotherapy in this setting.

Keywords High rectal cancer · Radiation therapy · Chemotherapy

This article is part of the Topical Collection on *Localized Colorectal Cancer*

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Introduction

Rectal cancer (RC) is the third most commonly diagnosed cancer and the third leading cause of cancer death in the USA [1•]. Defined by the National Cancer Institute as tumor occurring in the distal large bowel 12 cm or less from the anal verge by rigid proctoscopy, this malignancy will account for an estimated 39,220 new cases in 2016 ([2], http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf]). Locally advanced RC in the form of T3/4 disease, with or without nodal positivity, has historically shown high rates of local failure (up to 50 %) with surgery alone [3–5]. The series of local recurrence patterns have shown increased relapse in the mesorectum, presacral space, and anal triangle depending on the location within the rectum of the primary disease, with tumors in the middle and lower rectum resulting in higher recurrence rates [4, 6]. Lymphatic tumor spread has been found to drain primarily into the mesorectal lymph nodes as well as the nodes along the internal iliac artery, middle rectal artery, and obturator artery [6].

The treatment schema for locally advanced disease has evolved from surgery alone to surgery followed by postoperative adjuvant chemoradiation therapy (CRT) [7] to a neoadjuvant approach with total mesorectal excision (TME) as part of the oncologic resection [8]. With TME, the entire covering of the rectum containing its immediately adjacent vessels and nodes is removed en bloc, including the lateral extensions of the perirectal fat [9]. Although this surgical technique itself has been associated with decreased recurrence because it entails the removal of the field of spread of rectal cancer, local failures have also consistently been reduced with the incorporation of pelvic radiotherapy as well [10]. In the pre-TME era, pelvic radiotherapy alone not only reduced local recurrences with short-course radiation therapy (SC-RT) but also

improved overall survival, as long-term data from the Swedish Rectal Cancer Trial has shown [11]. The current standard of care in the TME era continues to include pelvic radiation therapy (RT), with either long-course chemoradiation (LC-CRT) or high dose of SC-RT alone, with multiple studies reporting a higher risk of recurrence in tumors closer to the anal verge [4, 11–14].

With high rates of distant metastatic disease still an ongoing concern in the multidisciplinary management of rectal cancer [15–17], the question thus becomes which patients can be reliably predicted to have the highest risk of local failure and which strategies would most effectively mitigate that risk, balancing the local control benefit of radiation with the treatment duration, toxicity, and volume of tissue irradiated. Finally, the issue of whether pelvic radiotherapy may be avoided in selected patients, either altogether or potentially with either a chemotherapy alone approach or with more targeted therapy directed to the tumor and immediate mesorectum, merits further exploration. This review will evaluate neoadjuvant strategies containing radiation to compare available outcome data in the context of tumors that are located in the upper rectum, 10 cm or greater from the anal verge.

Toxicity of Radiation

Identification of patients with a low risk of LR has become increasingly important in order to spare the subset of patients least likely to benefit from the toxicity associated with pelvic radiation. As the neoadjuvant randomized trials have matured, there has been increasing concern over the potential for cumulative gastrointestinal and sexual toxicities in patients receiving pelvic radiation.

Long-term follow-up of the Dutch Colorectal Cancer Group study found that patients who received preoperative RT compared to those who did not receive pre-op RT reported higher rates of the gastrointestinal toxicities of fecal incontinence (62 vs. 38 %, respectively; $P < 0.001$), pad wearing as a result of incontinence (56 vs. 33 %, respectively; $P < 0.001$), anal blood loss (11 vs. 3 %, respectively; $P = 0.004$), and mucus loss (27 vs. 15 %, respectively; $P = 0.005$) [18]. Sexual dysfunction has been reported to be increased after pelvic RT as well, with analysis by Marijen et al. of 990 patients who were randomized to either short-term RT (5 × 5 Gy) followed by TME or TME alone at 3, 6, 12, 18, and 24 months after surgery, noting worsening function in both men and women [19]. Although there were few significant differences in health-related quality of life between the two groups, there was a significant negative effect on sexual functioning in both males ($P = 0.004$) and females ($P < 0.001$) in the irradiated arm compared to the non-irradiated arm. In particular, preoperative RT was found to be significantly associated with ejaculation disorders ($P = 0.002$) and deterioration of erectile functioning over time ($P < 0.001$) in males. There was a significant increase in male sexual dysfunction in the arm that received preoperative RT, with dysfunction persisting from 6 months after surgery to 2 years after surgery ($P = 0.004$).

Neoadjuvant combined chemoradiation prior to surgery has also been associated with gastrointestinal toxicities and sexual dysfunction. Herman et al. [20] prospectively analyzed acute changes in patient-reported quality-of-life endpoints during and after preoperative CRT for rectal cancer. There was a significant decrease in global quality of life during treatment (−9.50, $P = 0.0024$), with gastrointestinal (nausea/vomiting +9.94, $P < 0.0001$; and diarrhea +16.67, $P = 0.0022$) and urinary (dysuria +13.33, $P < 0.0001$; and frequency +11.82, $P = 0.0006$) symptoms as well as fatigue (+16.22, $P < 0.0001$) comprising the majority of adverse effects. However, these symptoms returned to baseline only 1 month after CRT ended (−0.33, $P = 0.9205$). Sexual enjoyment ($P = 0.0236$) and sexual function ($P = 0.0047$), in contrast, remained significantly decreased following the CRT and persisted.

Additionally, neoadjuvant therapy has been found to cause adverse effects on fertility. Pelvic radiotherapy increases the risk of azoospermia [21] and reduces serum testosterone and increases serum levels of gonadotropins, which can result in permanent testicular dysfunction [22]. In women, low-dose radiation delivered to the oocyte can cause ovarian failure and infertility [23]. Moreover, women can also experience the late toxicity of radiation-induced menopause, vaginal stenosis, and the inability of the irradiated uterus to carry a fetus to term. Accordingly, the American Society of Clinical Oncology (ASCO) has developed guidelines on fertility preservation, suggesting that clinicians discuss this issue prior to the initiation of treatment with all patients of reproductive age, if infertility is a potential risk [24•].

Patient Selection for Neoadjuvant Therapy

Based on the prospective randomized data that has established the superior efficacy of preoperative pelvic RT in the treatment of RC and the concomitant potential for late gastrointestinal and sexual toxicities, focus has now shifted toward patient selection for neoadjuvant therapy—particularly, identification of risk factors for local recurrence. Although the primary factors considered in determining whether a patient is at high risk for recurrence, and will thus benefit from neoadjuvant therapy, include T and N stage, location of the tumor, and the CRM status, many authors have also reported poor differentiation, lymphovascular invasion, involvement of the circumferential margin, low-lying tumors, high pretreatment carcinoembryonic antigen, and invasion into the perirectal fat to be predictive of high local recurrence in arciorectal cancer [25]. Early studies in the pre-TME era evaluating the

outcomes of patients treated with resection alone with pathologic T3N0 tumors suggest that there is a subset of patients with favorable histology (well or moderate differentiation invading <2 mm into the perirectal fat without any lymphatic or venous invasion) with 10-year actuarial local control and recurrence free survival rates of 95 and 87 % [26].

An analysis of the outcomes of patients treated on large North American cooperative group adjuvant therapy trials in the early 2000s led to the distinction of three risk categories characterized as intermediate risk (T3N0, T1-2N1)/moderately high (T4N0, T1-2N2, T3N1)/and high (T3N2, T4N1, T4N2) [27]. Further patient data was reported a few years later when two additional adjuvant trials were pooled, confirming the initial findings, and reporting a 5-year local recurrence of 9 and 20 % distant metastasis rate for T3N0 patients and a 7 % rate of LR and 15 % rate of distant metastasis for T1-2N1 [28]. Neither pooled analysis had subset data on the distance from the anal verge. Improved outcome data for the intermediate risk category has been confirmed as well in a data set of over 35,000 patients included in the Surveillance, Epidemiology, and End Results (SEER) database [29].

Recurrence Risk and Tumor Distance from the Anal Verge

Recent interest has focused on identifying tumors that are at low risk of LR, suggesting that preoperative RT may only add toxicity without benefit. Several retrospective trials have been reported focusing on identifying low-risk patients based on the stage and various other clinical and pathological features (Table 1) [26, 30••, 31–34, 35••]. Wang et al. report on 166 pT3N0 rectal cancer patients with tumors 5–12 cm above the anal verge and with CRM >1 mm [30••]. Overall 3- and 5-year LR was 2.5 and 3.4 %, respectively. Patients with <12 LN removed at the time of surgery were at higher risk of LR ($P = 0.03$) as well as worse relapse free survival ($P = 0.05$). Park et al. looked at patients with stage IIA disease and compared outcomes [33]. Overall, radiotherapy had no effect on LR in relation to tumor location; however, patients with low tumors and with ≤16 LN had an overall increase in LR. Frasson et al. reported outcomes on 152 patients with cT2N+, cT3N0, and cT3N+ patients who did not receive preoperative CRT [32]. Significant factors associated with increased LR were preoperative threatened CRM (0.007), positive CRM on pathologic assessment ($P < 0.001$), and pathologic positive LN ($P = 0.04$). There was no significant difference in relation to tumor location (lower 1/3 11.1 % vs. mid to upper 2/3 6.1 %, $P = 0.52$), APR vs. LAR, or preoperative LN status. Chang et al. reported on patients with locally advanced upper rectal tumors [35••]. Overall, LR was 4.5 % in the whole cohort, 3 % for T1-2/N1, T3N0, 4.8 % in T1-2N2, T3N1, T4N0, and 8.7 % for T3N2 and T4N1-2. Furthermore, patients without sacral-side involvement and ≤5 mm mesorectal invasion had no LR. Lastly, Kim et al. report on stage IIA patients treated with TME followed by chemotherapy ($n = 29$) or chemoradiation ($n = 122$) [34]. No significant difference in LR was observed (3.4 vs. 9 %, $P = 0.35$). In this trial, positive CRM was associated with worse local control ($P = 0.002$) on multivariate analysis.

Mature prospective preoperative randomized trial data now can be compared to earlier pre-TME series and examine whether local recurrence risk is associated with tumor distance from the anal verge, as shown in Table 2. Typical cuttoffs for tumor location are less than 5 cm, 5–10 cm, and greater than 10 cm from the anal verge for low, mid, and high rectal cancers, respectively. One of the earliest reports examining this question was reported by Pilipshen et al. who retrospectively examined patterns of local and distant recurrences following resection for rectal cancer in 412 patients at Memorial Hospital, finding a significantly higher pelvic recurrence rate in low (30.7 %) and mid (30.1 %) tumors as compared to high (9.6 %) tumors, defined as 12 cm or higher from the anal verge ($P < 0.002$) [4]. In the prospective pre-TME Swedish Rectal Cancer Trial, the incidence of local recurrence was reduced with SC-RT at all tumor heights but was not statistically significant for tumors >10 cm from the anal verge [11]. Investigators found similar results in the 11-year follow-up of the German Rectal Cancer Trial, with the lowest local recurrence rates in patients with rectal cancers 10–16 cm above the anal verge and the highest rates in patients with cancers <5 cm, in both the pre-op CRT and post-op CRT groups [36]. The authors report the lowest risk of recurrence in neoadjuvant and adjuvant CRT patients with tumors 10–16 cm from the anal verge compared with patients that ended up not receiving CRT, with LR of 4.3 % preoperative, 2.7 % adjuvant, and 10.4 % no therapy, respectively. Sebag-Montefiore et al. compared pre-op RT with selective post-op CRT in 1350 patients with rectal cancer; in their multicenter, randomized trial, they found 3-year local recurrence rates of 4.8, 5, and 1.2 % in patients with rectal cancers 0–5 , 5–10, and 10–15 cm above the anal verge, respectively, in the pre-op RT group; these values were 10.4, 9.8, and 6.2 % in the selective post-op CRT group who were irradiated due to a positive margin [14].

In the 6-year follow-up of the Dutch TME trial, Peeters et al. found significantly lower local recurrence risk in patients with tumor location of 10 or more centimeters from the anal verge in both the TME + radiation group (3.7 %) and the TME alone group (6.2 %) compared to tumors lower than 10 cm [13]. Further, subgroup analysis showed that there was a significantly decreased LR rate for those tumors 5–10 cm from the anal verge that received SC-RT. On long-term follow-up, however, when excluding patients with a positive CRM, the relationship between location of the tumor and LR was non-significant ($P = 0.62$) [37]. The data from these trials indicate that pelvic radiation may potentially be

Table 1 Retrospective trials in patient selection for neoadjuvant therapy

Reference	Method	Results
Wang et al. [26]	Retrospective; $N=166$	–pT3N0 patients w/ tumors 5–12 cm above the anal verge and with CRM > 1 mm
		–Overall 3 and 5 year LR: 2.5 and 3.4 %
		–<12 LN removed at the time of surgery at higher risk of LR ($P=0.03$) and worse relapse free survival ($P=0.05$)
Merchant et al. [27]	Review of prospective database; $N=95$	–Lymphatic invasion significantly associated with local recurrence ($P<0.04$)
		–No other technical factors associated with local recurrence
Willett et al. [28]	$N=117$	–Differentiation, perirectal fat invasion, and lymphatic and/or vessel involvement significantly associated with 10-year local control and recurrence-free survival rates (95 and 87 %, respectively for favorable histology; 71 and 55 % for unfavorable histology)
Frasson et al. [29]	Prospective; $N=152$	–cT2N+, cT3N0, and cT3N+ patients who did not receive preoperative CRT
		–Preoperative threatened CRM (0.007), positive CRM on pathologic assessment ($P<0.001$), and pathologic positive LN ($P=0.04$) associated with increased LR
		–No significant difference w/ tumor location (lower 1/3 11.1 % vs. mid to upper 2/3 6.1 %, $P=0.52$), APR vs. LAR, or preoperative LN status
Park et al. [30••]	Retrospective; $N=390$	–Stage IIA patients
		–Low tumors associated with overall increase in local recurrence
		–Patients with ≤16 LN removed at increased risk of local recurrence
Kim et al. [31]	Prospective, observational; $N=151$	–Stage IIA pts. treated with TME followed by CT ($n=29$) or CRT ($n=122$).
		–No significant difference in LR (3.4 vs. 9 %, $P=0.35$).
		–Positive CRM associated with worse local control ($P=0.002$)
Chang et al. [32]	Retrospective; $N=110$	–Locally advanced upper rectal tumors
		–LR rates: 3 % for T1-2/N1, T3N0; 4.8 % in T1-2 N2, T3N1, T4N0; and 8.7 % for T3N2 and T4N1-2
		–Pts. w/o sacral-side involvement and ≤5 mm mesorectal invasion had no LR

spared in patients with high rectal cancers as this group is at lowest risk for local recurrence and the benefit of RT in this subgroup is not clear.

Efficacy of Diagnostic Imaging Tools

The risk of over treatment (or under treatment) is largely dependent on the accuracy of diagnostic tools used in preoperative staging to determine those high cancers that would be at the highest risk for local failure. A series from Memorial Sloan-Kettering [38] reported that the efficacy of ERUS/MRI in the preoperative setting is limited, with up to 22 % of patients originally staged as cT3N0 actually having undetected mesorectal LN involvement, and 19 % being overstaged and therefore overtreated. In the study by Park et al., 37 % of patients staged as cT3N0 by either TRUS or MRI had pathologic mesorectal LNs [39•].

Despite the difficulty of detecting nodal involvement, MRI has been shown to be reliably capable of predicting other prognostic criteria [40]. The MERCURY study group reported on 408 patients with MRI used to predict CRM [41]. They found that 94 % of patients predicted to have a clear CRM did so at the time of surgery, and the overall accuracy of all patients was 88 %. Of the patients treated with primary surgery, MRI accurately predicted clear margins in 91 % compared to 77 % of those that received preoperative CRT prior to surgery. Moreover, MRI defined "good" prognosis cancers treated with surgery alone in the MERCURY trial had a LR of 3 % [42]. Chang et al. identified high-risk patients with upper rectal cancers by MRI [35••]. MVA demonstrated the presence of both sacral side location and mesorectal invasion >5 mm to be associated with adverse DFS and OS. Patients who did not have these characteristics did not experience a LR. With the incorporation of better MRI and TRUS techniques into the

Table 2 Local recurrence risk based on the distance from the anal verge

Reference	Method	Results
Pilipshen et al. [4]	Retrospective; $N=412$	Pelvic recurrence by tumor location ($P<0.002$): –0–5 cm: 39/127 (30.7 %) –6–11 cm: 61/203 (30.1 %) –≥12 cm: 5/52 (9.6 %)
Folkesson et al. [11]	Randomized; $N=1168$	Radiotherapy and surgery vs. surgery alone: –≤5 cm: 14/136 (10 %) vs. 39/146 (27 %);$P=0.003$ –6–10 cm: 16/185 (9 %) vs. 51/198 (26 %); $P<0.001$ –≥11 cm: 10/133 (8 %) vs. 13/110 (12 %); $P=0.3$
Sauer et al. [23]	Randomized; $N=823$	Pre-op CRT vs. post-op CRT vs. no CRT local recurrence at 10 years –<5 cm: 10.1 vs. 16 vs. 4.5 % –5–<10 cm: 4.9 vs. 9.3 vs. 18.7 % –10–16 cm: 4.3 vs. 2.7 vs. 10.4 %
Sebag-Montefiore et al. [14]	Randomized, multicenter; $N=1350$	3-year local recurrence by tumor position (cm) (pre-op RT vs. selective post-op CRT) –0–5: 4.8 vs. 10.4 % (HR = 0.45) –>5–10: 5 vs. 9.8 % (HR = 0.5) –>10–15: 1.2 vs. 6.2 % (HR = 0.19)
Gunderson et al. [12]	$N=75$	Incidence of pelvic failure vs. level of initial lesion (cm) –0–5: 15/28 (53.6 %) –6–10: 12/22 (54.5 %) –>10: 8/15 (53.3 %)
Peeters et al. [13]	Randomized; $N=1861$	LR risk in patients who underwent TME + RT vs. TME alone based on distance (cm) from the anal verge –≤5: 10.7 vs. 12 % ($P=0.578$) –5.1–10: 3.7 vs. 13.7 % ($P<0.001$) –≥10: 3.7 vs. 6.2 % (P=0.12)

preoperative workup schemas, reproducible identification of high-risk proximal rectal tumors may soon be feasible.

Treatment Volume: Time to Tailor?

The earlier randomized trials had standard field borders based on bony anatomy, with initial trials extending from L5/S1 to 1 cm below the anal verge. Modern CT-based contouring guidelines now exist that recommend elective coverage of the mesorectal, presacral, and internal iliac regions for all locally advanced patients with the additional external iliac region for patients with T4 lesions [43]. Current guidelines do not alter the treatment volume based on tumor location within the rectum. However, Syk et al. [44] noted in a series of patients with rectal cancer LR, which tumors >10 cm from the anal verge had no signs of lateral recurrence, suggesting that it may be possible to exclude full coverage of the internal iliac nodes and obturator nodes for high tumors. The inferior border may be tailored as well, with data showing that the anal sphincter complex can be omitted in tumors >6 cm from the anal verge, with potentially a more limited mesorectal coverage for the highest tumors >10 cm since surgical series have shown tumor deposits in the mesorectum 4 cm or less from the primary tumor [45].

Since the toxicity of the current standard of care of pelvic RT regimens is secondary to the large volume of normal tissue irradiated, then strategies for tailoring the treatment volume for high pelvic tumors may be feasible while maintaining the local control benefit. Data supporting such an approach may be considered from the work of Vuong et al. with the delivery of radiation to the tumor and mesorectum only with an endoluminal brachytherapy (EBT) approach [46••, 47]. This mode of RT, which omits routine pelvic irradiation, allows for the

delivery of extremely high doses of radiation directly to the tumor through direct contact with radioactive sources, completely sparing adjacent normal structures [47]. The most recent update of the EBT experience at McGill University in Montreal has been published, reporting on EBT for patients with locally advanced rectal cancer [46••]. The local recurrence rate was reported as 5 % in this EBT study and, compared with 5 % in the Dutch trial, was despite the fact that only 1/3 of patients in the McGill study underwent a TME surgery.

EBT thus raises important questions about the benefits of inclusion of elective pelvic lymph nodes since the reported LR is similar to the randomized trials that included pelvic irradiation. These data suggest that prospective comparison of radiation treatment volume is warranted, especially since much of the toxicity concerns could be greatly reduced with a target volume encompassing the primary tumor and adjacent mesorectum only.

Current Guidelines

Based on available current data, the American Society for Radiation Oncology (ASTRO) has released clinical practice appropriateness criteria [15]. Patients were divided into intermediate risk (T1-2N1 or T3N0), moderately high risk (T1-2N2, T3N1, or T4N0), and high-risk (T3N2 and T4N1-2) categories. For neoadjuvant therapy, LC-CRT was rated as *appropriate* in all risk groups. SC-RT was rated appropriate for intermediate risk ≤10 cm from the anal verge and ≥2 mm from the edge of the mesorectal fascia and for moderate risk disease <5 cm from the anal verge and ≥2 mm from the mesorectal fascia edge. Neoadjuvant chemotherapy (CT) alone was rated as *may be appropriate* for the selection of intermediate and moderate risk disease patients with non-threatened mesorectal fascia. Endorectal brachytherapy (EBT) was rated as *rarely appropriate* in any category and no neoadjuvant therapy was considered *rarely appropriate* to *may be appropriate* based on the distance from the mesorectal fascia and anal verge.

In the adjuvant setting, patients with negative margins and intermediate risk disease, CRT and CT were rated *appropriate*, except in tumors >10 cm from the anal verge, where the panel rated the recommendation as *may be appropriate*. For patients with moderately high-risk tumors and negative margins, adjuvant CRT and CT were *appropriate* in all cases but there was less consensus for tumors >10 cm from the anal verge. CT alone was rated as *appropriate* for tumors >10 cm from the anal verge and *may be appropriate* for more distal tumors. For high-risk tumors and negative margins, CRT in conjunction with CT was rated *appropriate* and CT alone was *may be appropriate*.

Conclusion

Standard management of patients with locally advanced rectal cancer consists of neoadjuvant therapy, either with short-course RT or long-course combined CRT, followed by TME containing oncologic tumor resection. In a disease with high rates of distant metastases for locally advanced tumors, the growing body of literature on GI toxicities and fertility loss associated with pelvic radiation has incited the search for more tailored treatment approaches based on individual tumor risk for LR. Since the risk of local recurrence for proximal rectal cancers is less than that of lower rectal cancers, prospective confirmation of low-risk patients is needed to determine who can safely omit pelvic radiotherapy. An improvement in accurate preoperative identification of risk is thus needed. Omission of pelvic radiotherapy for those high tumors at lowest risk for LR can be considered, with future research directed at optimizing the volume of tissue irradiated based on relative recurrence risk to retain the local control benefit while minimizing toxicity.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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