Review Article

Neoadjuvant chemoradiation therapy for rectal cancer: current status and perspectives for the surgeon

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Abstract: Modern management of rectal cancer has become increasingly complex over the last decades. The introduction of neoadjuvant chemoradiation to the treatment strategy of locally advanced and distal rectal cancers has added numerous variables that may ultimately affect final surgical or even non-surgical management. Specific chemoradiation regimens, intervals after neoadjuvant treatment completion and tools for the assessment of tumor response may all affect final surgical decision and should be interpreted with care. The present study attempts to provide a review of commonly used neoadjuvant chemoradiation regimens, specific intervals and final surgical or non-surgical management of rectal cancer in current clinical practice.

Keywords: Rectal cancer; neoadjuvant therapy; total mesorectal excision (TME)

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Introduction

Significant changes in the clinical management of rectal cancer over the past 15 years have occurred. Prior perioperative chemotherapy or radiation therapy, recurrence rates could reach 40% in patients with locally advanced rectal cancers (1). Over the years, the increasing importance given to pre- and post-treatment staging, pre-operative multimodal treatment, new surgical techniques and detailed pathological analyses has contributed to improvement in the treatment and survival of these patients. Therefore, the management of patients with rectal cancer has become multidisciplinary requiring a coordinated effort from physicians and surgeons and with regular multidisciplinary requiring a coordinated effort from multiple specialties and with regular meetings as the best way to obtain synchronization (2).

The changes incorporated in the management of advanced rectal cancer have emphasized a more individualized approach aiming to provide oncological safety preserving functional outcomes and quality of life. Alongside with the establishment of total mesorectal excision (TME) (3), one of the most important interventions pertains the use of chemoradiation therapy (CRT), which has been part of the treatment of rectal cancer since the 1990s. Therefore, treatments potentially associated with decreased morbidity, improved functional and quality of life outcomes are of significant interest to patients and payer stakeholders (4).

In the following pages, we review the current evidence on the present and future use of CRT in the treatment of patients with locally advanced rectal cancer.

First things first: the role of TME

For patients with advanced rectal cancer, surgery remains the

pillar of curative treatment. Complete TME accomplished through an appropriate surgical technique is required to assure adequate oncological outcomes and minimize intra and postoperative complications (5,6). A precise dissection between the visceral mesorectal fascia and the parietal endopelvic fascia using a conventional or minimally invasive approach enables complete *en bloc* removal of the primary tumor and associated mesorectal lymph nodes. Proper TME also prevents autonomic nerve injuries and intraoperative bleeding. This operation should be conducted by experienced surgeons in the management of rectal cancer, with lower complication rates and improved survival (7).

One of the major determinants for local recurrence is the presence of neoplastic foci within parts of mesorectum left behind (non-resected) (5). Distal mesorectal spread often extends further than intramural spread, resulting in nests of cancer cells away from the primary tumor as far as 3 to 4 cm (8). Therefore, in upper rectal tumors, the mesorectal excision (also called tumor-specific or partial) should extend at least for 5 cm beyond the distal edge of the primary tumor, whereas TME is required mid and low rectal tumor (9). These issues were addressed by Heald *et al.* with the first description of TME reported in 1982 (3). TME alone in selected cases may provide rates of local recurrence as low as 5–10%.

Another crucial surrogate marker used for local control is obtaining an adequate circumferential radial margin (CRM). Addressed in the pre-treatment staging most commonly through dedicated high-resolution magnetic resonance, imaging studies are mandatory for TME planning and decision for the need of neoadjuvant therapy (10). A pathologically compromised (≤1 mm) circumferential resection margin [(+) CRM] is an independent predictor of local recurrence and decreased survival (5).

Neoadjuvant chemoradiation therapy (nCRT): since when and why?

Multimodality treatment, instead of surgery alone, was initially given postoperatively, for the curative treatment of locally advanced rectal cancer. Before broad adoption and practice of TME surgery, multimodality therapy had become standard for patients with locally advanced rectal cancers (2). The efficacy of postoperative CRT was demonstrated in the GTSG and NSABP R-01 trials (11,12). In the GTSG-7175 study, it was observed a significant decrease in the overall recurrence rate after adjuvant CRT when compared to the surgery alone group (33% *vs.* 55%) (11). Despite not showing a difference in overall survival (OS) among groups, the CRT group had a longer time to (tumor) recurrence. Conversely, in the NSABP R-01 trial, in which surgery alone was compared with surgery plus adjuvant radiation or plus adjuvant chemotherapy, patients treated with adjuvant chemotherapy had an improved disease-free survival (DFS), despite similar rates of local or distant recurrences (12). The results of these two studies formed the basis for the 1990 U.S. National Cancer Institute Consensus Statement, that recommended adjuvant therapy for stage II and III rectal cancer (13). It was not before 1991 that the first study reporting benefits of adjuvant CRT for decreasing local recurrence rates and prolonging 5-year overall and DFS was published (14).

The initial considerations among investigators regarding neoadjuvant CRT (nCRT) was based on its potential to promote primary tumor and lymph nodes downstaging in a more oxygenated and unscarred tumor tissue allowing easier resection and eventually increasing the chance of sphincter-preserving surgery. Additional benefits included decreased toxicity due to smaller volume of irradiated small bowel, and improved functional outcomes for not irradiating a low colorectal or coloanal anastomosis.

Neoadjuvant therapy for rectal cancer is accomplished more commonly by selecting one of two main strategies: preoperative short-course radiotherapy (SCRT), and long-course nCRT. The SCRT consists of 5 Grays (Gy) of external beam radiotherapy delivered daily for 5 days (5×5 Gy) without chemotherapy and surgery performed within 1 week. In the long-course nCRT, preoperative external beam RT using 1.8 to 2 Gy daily doses are delivered with concurrent administration of 5-fluorouracil-based chemotherapy over 5–6 weeks. The full dose reaches 45 to 50.4 Gy and is followed by radical surgery after 8–12 weeks of resting period.

The Swedish Rectal Cancer Trial reported that patients submitted to SCRT have a lower recurrence rate (11% *vs.* 27%), a higher 5-yr OS (58% *vs.* 48%; 75 months follow-up), and cancer-specific survival at 9 years (74% *vs.* 65%) when compared to patients without radiotherapy (15). Moreover, better long-term oncologic outcomes were confirmed in a later update (16). A survival benefit for rectal cancer patients assigned to preoperative SCRT remains exclusively associated with this trial. As TME was not the standard technique during this trial, the external validity of the Swedish trial is difficult to estimate, especially if we highlight a 27% local recurrence rate in the surgery alone group.

Meanwhile, the Dutch TME trial also demonstrated better local control after 2 and 10 years for tumors located below 10 cm from the anal verge, when comparing SCRT and TME alone (17,18). However no impact on OS was observed. Moreover, if we consider a subgroup analysis of patients with pathological stage III rectal cancer undergoing TME and negative CRM, survival was better after 10 years (50% *vs.* 40%; P=0.032) in the SCRT group.

The next logical step would be to verify the potential advantages of neoadjuvant compared to adjuvant CRT. The German trial randomized patients to nCRT and TME or TME followed by adjuvant CRT (19). The experimental group treatment consisted of 5,040 cGy, concurrently with infusional 5-FU. All patients underwent TME 6 weeks after the completion of CRT and had 4 additional cycles of adjuvant 5-FU, one month after TME. The control group had identical postoperative treatment, except for the delivery of a 540 cGy boost in this group. Those that received nCRT had significantly lowered 5-yr (6% *vs.* 13%; P=0.006) and 10-yr local recurrence rates (7% *vs.* 10%; P=0.048) (19,20). Distant recurrence, overall, and DFS rates were similar between the two groups. Downstaging was significantly more frequent in the preoperative group as expected. In the nCRT group, 8% had developed pathologic complete response (pCR), and 25% had positive lymph nodes (40% in the postoperative group). In addition to the benefits in final pathological staging, the preoperative group had a higher chance of completing the treatment than the control group.

Although two other trials aimed to compare nCRT with postoperative CRT in the U.S., both the Radiation Therapy Oncology Group and the National Surgical Adjuvant Breast and Bowel Project were prematurely terminated due to insufficient accrual.

Current evidence supports that, combined with radical surgery, nCRT for advanced rectal cancer, results in a statistically significant reduction in local recurrence rates. Additionally, long-course CRT may reduce the odds for a CRM+ and may positively impact the rates of sphincter-preserving operation even though there is still insufficient evidence to fully support this (21). Altogether, following the publication of the German Trial, long-course nCRT became the new standard of care for patients with advanced rectal cancer.

nCRT: how? Short- versus long-course nCRT

An alternative strategy to long-course nCRT is the use of SCRT for the treatment of patients with operable rectal cancer, as previously reported by the Swedish and Dutch studies. A shorter neoadjuvant approach at a reduced cost are main attractive when considering SCRT.

The comparison of clinical results between SCRT and nCRT was addressed in two main trials.

In the Polish trial, no difference regarding sphincter-preserving rates was observed between the two groups (respectively, 61.2% and 58%). However, long-course nCRT was associated with more tumor donwnstaging (pCR: 16.1% after nCRT *vs.* 0.7% after neoadjuvant SCRT) and a lower rate of (+) CRM (12.9% *vs.* 4.4%) (22). In the long-term follow-up no difference was observed between the groups regarding local recurrence and overall survival. It is important to notice though that this trial was designed to evaluate if long-course CRT could lead to more sphincter-preserving surgery, and was not properly powered to evaluate difference regarding recurrence and survival. Despite meaningful downsizing, long-course nCRT did not result in increased sphincter preservation rate. The issue of defining the type of operation to be performed based on pre-multimodality treatment tumor characteristics may have certainly contributed to the results of this trial.

In the Trans-Tasman Radiation Oncology Group (TROG) Trial, the main outcome was local recurrence after treatment. Also in this study no difference was observed among the two groups in local or distant recurrence rates and overall survival. Again, after long-course nCRT, tumor downstaging was more frequently observed. However, when Annual Percentage Rates (APRs) are considered in each treatment, as observed in the Polish trial, no benefit (79% *vs.* 77%) could be attributed to a long-course treatment (23).

According to the MERCURY trial, magnetic resonance imaging (MRI) may have established standards for the identification of patients with high-risk rectal cancers (24). For patients with clearly resectable cancers, TME alone may provide excellent local and systemic control. On the other hand, for patients harboring features associated with a high risk for local recurrence, long-course nCRT remains the preferred option. Finally, in an intermediate group, SCRT followed by immediate surgery is an undeniably clever strategy.

The main drawback for nCRT is treatment-related toxicity, especially in frail patients. The efforts in avoiding toxicity, by omitting chemotherapeutic agents may negatively affect efficacy. Ultimately, since there is significant morbidity associated with radical surgery for rectal cancer, complicated cases may not be fit enough

to receive adjuvant chemotherapy leading to low overall compliance rates.

Despite the disadvantages of long-course nCRT toxicity, SCRT is still not the new standard of care (25). In the currently ongoing RAPIDO trial, patients with high-risk rectal cancer as determined by MRI are randomized to nCRT (25×1.8 or 25×2 Gy with capecitabine) and selective postoperative adjuvant chemotherapy or SCRT (5×5 Gy) followed by full-dose chemotherapy (26). These results may significantly contribute to the understanding of current options in neoadjuvant therapy.

Optimal interval between nCRT and radical surgery: pursuing pCR

In an attempt to increase tumor response to nCRT and the rates of pCR, some groups proposed to increase the interval between CRT and radical surgery. Most commonly, TME has been recommended 6–8 weeks after CRT completion to maximize tumor regression and avoid extensive fibrosis (27-30). However, several studies have shown that longer intervals between CRT and surgery may increase the rates of pCR without increasing perioperative complications or worsening the oncologic outcomes (27,29,30). This is still a matter of debate in rectal management, without agreement over which is the best interval.

The issue concerning the interval between nCRT completion and radical operation exists for a long time. In the Lyon R90-01 Trial, patients were randomized to be operated after 2 or 6 weeks after CRT completion (31). Clinical response increased from 53.1% to 71.7% in the group randomized for longer interval. Since these results were published, 6 weeks become the standard of interval for operation after CRT.

However this interval did not seem enough. In 2004, Moore *et al.* have shown that the rate of pCR increased from 9% to 23% comparing patients operated before 6 weeks after nCRT completion and those that waited more than 7 weeks (27). A few years later, Tulchinsky *et al.* demonstrated that the pCR rates were higher after a longer (>7 *vs.* ≤7 weeks) interval between nCRT completion and surgery: 35% *vs.* 17% (P=0.03). And that those patients operated after 7 weeks had significantly better DFS (P=0.05) (28).

Habr-Gama *et al.* waited longer in their retrospective study comparing patients operated ≤12 weeks with those operated >12 weeks from nCRT completion (30). They observed similar rates of OS and DFS suggesting the safety of this approach. Also Kalady *et al.* observed higher rates of pCR when waiting longer than 8 weeks, and that these patients had better OS and local recurrence-free survival after 5 years than patients with incomplete response (32). Moreover, the local recurrence rate after 3 years was significant lower in the >8 weeks group (1.2% *vs.* 3.9%). Ultimately, the same group observed that the postoperative morbidity or mortality were similar between the two groups (29).

Probst *et al.* have published a retrospective observational study comprising information from the U.S. National Cancer Data Base (33). In this study, the association between interval time and pCR, surgical morbidity and tumor downstaging were evaluated in 17,255 patients using different cut-offs (<6, 6–8, >8 weeks). Longer interval was associated with higher pCR rates and tumor downstaging.

Even though a significant amount of retrospective studies supported the potential benefits of prolonged intervals between CRT completion and surgery, the recently reported results from the GRECCAR-6 study has reported rather disappointing outcomes. The comparison between 7 and 11 weeks after CRT completion and radical surgery not only resulted in no differences in pCR rates but also showed inferior outcomes for the 11 weeks interval group in terms of quality of the mesorectum and postoperative morbidity (34).

After standardization of multimodality treatment and proper TME surgery, the development of distant relapse became more relevant than local recurrence. Consequently, postoperative adjuvant chemotherapy should be recommended at least to some (if not all) patients treated with nCRT. However up to 27% of patients eligible to adjuvant chemotherapy never actually receive treatment as a significant amount of patients fail to receive the full-prescribed treatment due to postoperative complications or stoma closure. A systematic review including more than 15,000 patients demonstrated that a 4-week delay in treatment is correlated with a 14% decrease in OS (35). Moreover, the use of chemotherapy in the resting period between nCRT completion and response assessment could potentially increase rates of clinical complete response (cCR). Habr-Gama *et al.* added chemotherapy during this interval, demonstrating an increased rate of cCR. In this prospective study, 34 patients with rectal cancer underwent radiation and 5-fluorouracil-based chemotherapy every 21 days in six cycles (36). The complete response rate was 65% for at least 12 months after nCRT. The authors concluded, although in a preliminary basis, that the addition of chemotherapy during the resting period (also known as

"consolidation" chemotherapy) and after nCRT resulted in considerably high rates of complete response.

Patients harboring tumors that achieve a pCR after nCRT have a better prognosis than the non-responders. In these patients, local recurrence is uncommon and survival is excellent. However, response to chemoradiation is variable. Moreover, the proportion of patients achieving a pCR remains not only unpredictable, but small. Garcia-Aguilar *et al.* conducted a non-randomized trial adding cycles of mFOLFOX6 between nCRT and surgery (37). In the group without additional mFOLFOX6 cycles 18% of patients achieved pCR. In the groups of patients receiving two, four, or six cycles of mFOLFOX6 the pCR rates were 25%, 30%, and 38% respectively.

Current recommendation suggests surgery to be scheduled after 6 to 8 weeks following nCRT completion as the standard. Still, optimal timing of surgery remains controversial with evidence supporting that longer interval may increase tumor downsizing.

Complete clinical response after nCRT and the watch and wait (WW) strategy

nCRT for rectal cancer may result in significant primary tumor downstaging. In fact, the degree of tumor downstaging may lead to clinically relevant consequences in terms of long-term oncologic outcomes. Survival and local disease control seem to be directly related to tumor regression, while complete pathological response is clearly associated with improved oncological outcomes (38). Radical surgery remains the cornerstone of the treatment of patients with locally advanced rectal cancer. However, up to 33% of patients treated with nCRT exhibit a pCR at the time of surgical resection (31). In the setting of a pCR, local recurrence rates lower than 1% and 5-year survival rate higher than 95% lead us to question the true benefit of TME for these patients (38). Moreover, tumor downstaging and pCR may offer the possibility of sparing patients from significant postoperative morbidity associated with TME, avoidance of a definitive stoma or even the need of any surgical resection with an organ-preserving strategy. Also known as the WW approach, it was pioneered in an institutional level in Sao Paulo (39-42).

Regarding radical surgery for rectal cancer after nCRT, several perioperative complications, including vascular injury and presacral bleeding, infection, wound complications, ureteral injury, and both urinary and sexual dysfunction, are associated with this procedure (43). The Dutch TME trial observed in-hospital postoperative mortality and overall complication rates of 3% and 47%, respectively (17,44).

If there is not a viable cancer cell left after nCRT, then radical surgery may not add a clinical benefit at the expense of adding risk for increased morbidity (45). WW precludes pathologic confirmation of the primary tumor and lymph node response. As a result, a cCR is used as a surrogate for pCR. The determination of a cCR is defined after assessment through a combination of digital rectal examination, direct visualization by proctoscopy, and imaging studies with or without biopsy confirmation. The definition of a complete clinical response should be based on strict clinical and endoscopic findings. The finding of any residual superficial ulceration, irregularity, or nodule should prompt surgical attention, including transanal full-thickness excision or even a radical resection with TME. Standard or incisional biopsies should be avoided in this setting (46). Endorectal ultrasound (ERUS) imaging and MRI are useful techniques for rectal cancer staging. In one meta-analysis, ERUS was found to have increased sensitivity for perirectal tissue invasion in comparison with MRI (90% *vs.* 82%). However, regarding imaging of lymph node involvement, both methods had similar rates of sensitivity and specificity (66–67% and 76–78%, respectively) (47). In contrast to the results of baseline imaging evaluation, in a meta-analysis both techniques overstaged (73% and 66%) patients with pCR (ypT0), respectively (48), and also had a poor sensitivity (MRI, 15%; ERUS, 37%) but high specificity (95% for both). Moreover, the accuracy for nodal restaging for both MRI and ERUS has been reported to be approximately 72% (48).

The experience with WW for potentially curable advanced rectal cancer has evolved with time. Most patients in early studies were not staged or followed with modern imaging techniques, including MRI and ERUS, mainly because these techniques were not widely available. Therefore, the assessment of cCR was almost exclusively based on clinical/endoscopic examination. Habr-Gama *et al.* defined that the follow-up of cCR demands intensive follow-up evaluations every 8 weeks after nCRT completion (46). Moreover, a 1-year disease-free interval has been arbitrarily defined in earlier studies for the classification of a cCR in order to rule out early regrowths requiring immediate salvage procedures.

In an early publication, Habr-Gama *et al.* reported the outcomes of 265 patients with distal rectal adenocarcinoma treated with nCRT (5,040 cGy with infusional

5-fluorouracil) (40). Only 26.8% of patients had cCR, 2.8% of patients developed an endoluminal recurrence, successfully salvaged, and 4.2% metastatic disease (57 months follow-up). A larger report confirmed the safety of this approach (42).

Following the published experience regarding WW led by the group of Sao Paulo, other institutions have reported small series regarding multimodality treatment of locally advanced rectal cancer without immediate surgery. Maas *et al.* using MRI found that only 11% of patients were eligible for WW. These patients had a 2-year DFS (89% *vs.* 93%) and OS rates (100% *vs.* 91%) similar to pCR patients. Patients who were treated operatively had more bowel dysfunction.

Appelt *et al.* prospectively evaluated patients with resectable distal rectal adenocarcinoma (49). In this trial, patients underwent high-dose external beam radiation therapy (60 Gy with a 5-Gy endorectal boost) and oral tegafur-uracil. Seventy-eight percent of patients diagnosed with cCR were initially managed without radical surgery. Cumulative local recurrence rates were 15% and 26% for 1- and 2-year follow-up. All patients were surgically salvaged.

Smith *et al.* reported the outcomes of 32 patients with rectal cancer after a 28-month follow-up. Local recurrence for WW group was 21% versus 0% in patients with pCR treated at the same institution (50). Successful salvage surgery was performed on all patients with local failure and outcomes were similar between the groups. This updated data from 73 patients achieving cCR, showed local tumor regrowth in 26% (3.5 years follow-up) and almost all patients were surgically salvaged. Rectal preservation rate for the series was 77%. Overall and DFS were similar between groups.

Habr-Gama *et al.* published the results of 70 patients treated with extended nCRT (also referred to as consolidation nCRT) chemotherapy (51). Forty-seven out of 69 (68%) patients that completed the treatment had cCR 10 weeks after nCRT. Of these, 39 sustained cCR for 12 months. Four developed local recurrence more than one year after nCRT. Overall, 35 (50%) patients have not undergone surgery after a median follow-up of nearly 4 years.

A significant proportion of patients with initial cCR may still develop local failure during the first 12 months of follow-up meaning that significant improvements in appropriate identification of cCR are warranted.

More recently, the OnCoRe project evaluated the acceptance of WW in what they have called "a real world multicentric setting". In this trial, 109 patients who developed cCR after nCRT were managed with no immediate surgery and 109 patients were operated. Patients not operated on immediately had a slight difference in 3-year DFS (88% *vs.* 78 and better colostomy-free survival (74% *vs.* 47%).

Despite these favorable experiences with no immediate surgery after a complete clinical response following nCRT, two studies have been reported recently attempting to caution the use of this WW approach. By querying the National Cancer Database (NCDB) in the U.S., Ellis *et al.* have tried to correlate the absence of surgical resection after nCRT with low-volume centers, uninsured patients and worse long-term survival. However, these studies underscore the importance of restricting such approach only to highly selected patients with thorough assessment of response after nCRT and achieving a complete clinical response. In the NCDB, no information is available regarding tumor response and it is likely that patients in both studies never underwent surgery for reasons other than presenting a cCR. In other words, no surgery after nCRT is very different from no immediate surgery after complete clinical response following nCRT (52-55).

Finally, efforts have been made to minimize the use of neoadjuvant RT. After the experience with exclusively chemotherapy for metastatic disease, the PROSPECT study is investigating the impact of neoadjuvant chemotherapy alone for locally advanced rectal cancer. Patients that develop favorable response to chemotherapy alone may undergo radical surgery or even WW (if complete clinical response is achieved) while only poor responders to chemotherapy are still referred to further (standard) CRT. The idea of delivering upfront chemotherapy is to address micrometastatic disease in addition to avoid the potential disadvantages of radiation therapy to the pelvis. Preliminary data have reported promising outcomes with nearly 30% complete pathological response rate (56).

Conclusions

In conclusion, management of rectal cancer has evolved significantly over the past decades and requires a multidisciplinary approach. Even though local control is now more easily achieved with proper surgical resection, neoadjuvant approaches may provide significant tumor regression allowing for organ-preserving strategies, provided assessment of tumor response shows evidence of complete tumor regression. Future studies addressing

oncological and functional outcomes with these various treatment strategies are warranted to further optimize the roles of surgery, radiation and chemotherapy in this setting.

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Footnote

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