24 Principles of Adjuvant and Neoadjuvant Therapy for Locally Advanced Rectal Cancer

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Introduction

Over 39,000 individuals are diagnosed with rectal cancer in the United States annually with an overall mortality rate of 35% [1]. Approximately half of these patients present as locally advanced rectal cancer (LARC) defined as T3/4 with or without nodal involvement in the absence of distant metastasis [2, 3].

During the past few decades, there have been significant advancements in the care of rectal cancer patients, attempting to reduce the rates of local recurrences and improve survival outcomes, with the intended added attempt to increase sphincter preservation rates. This evolution has essentially occurred through improvements in surgical technique with the establishment of the widely adopted total mesorectal excision (TME) [4], as well as the development of adjuvant therapy regimens. The current standard of treatment employs multidisciplinary approaches through the improvements in diagnostic and staging assessments that are then used to guide medical, radiation and surgical management of this patient population. Overall, this approach has been shown to result in a 70% decrease in locoregional recurrences and an improvement in the quality of care [5, 6]. Various neoadjuvant treatment modalities have been combined with the standardized TME approach to proctectomy for patients with LARC [7–9]. Unfortunately, after more than 10 years of follow-up, this multimodal strategy has failed to show improvements in systemic recurrences, disease-free survival (DFS) or overall survival (OS) with advantages mainly seen in the area of local recurrences [10, 11].

This chapter will summarize the various components of the multimodal treatment of LARC based on the current available evidence. We will also discuss the current controversies in this field while highlighting the evolving role of individualized care to improve oncological outcomes while preserving the quality of life in patients with LARC.

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Locally Advanced Rectal Cancer

Total Mesorectal Excision

Prior to the advent of perioperative chemotherapy or radiation therapy, the local recurrence rates in LARC were as high as 40% [12]. Efforts to address this high local recurrence led to two seemingly different yet highly interlinked approaches. One movement focused on the enhancement of perioperative adjuvant therapy whereas the other, equally important approach focused on improving the surgical technique itself [13]. The latter was advocated by professor Richard "Bill" Heald from Basingstoke, UK, who gave total mesorectal excision in rectal cancer widespread attention in 1979 [14, 15]. In his article, Dr. Heald emphasized the importance of the direct visualization and resection of an intact mesorecum by sharp dissection along the visceral and parietal pelvic fascial planes while mobilizing the rectum [14]. This technique would theoretically allow for the removal of potential residual tumors in an otherwise retained and intact mesorectum which has been postulated to be one of the causes of local recurrence after rectal cancer surgery [16, 17]. Indeed, the adoption of this surgical technique by itself, irrespective of the administration of adjuvant treatment, has led to a reduction in local recurrence rates to as low as 5–10% [13].

Neoadjuvant Therapy

Neoadjuvant therapy is defined as the administration of medical or radiation adjuncts to treatment in the pre-operative setting [18]. In the past, local recurrence rates of LARC occurred as high as 40% of the time [12]. However, with the advent of neoadjuvant therapy as well as standardized TME surgery, this rate has been dropped to as low as 5–10% in some series of patients with LARC [19, 20].

Neoadjuvant therapy in the form of radiosensitizing chemotherapy and external beam radiation has become a standard component of the multimodal treatment in LARC. Although this strategy has resulted in significant improvements in local recurrence rates, studies have yet to demonstrate consistent disease-free or overall survival benefits [13]. One of the seminal studies to demonstrate a benefit to the addition of chemotherapy with neoadjuvant radiation was the multi-arm randomized controlled trial of European Organization for Treatment of Cancer Radiotherapy Study group (EORTC 22921). In this study, the authors randomized 1011 patients with T3/T4 rectal cancer into one of four arms: pre-operative radiotherapy, pre-operative chemoradiotherapy, pre-operative radiotherapy with post-operative chemotherapy, and pre-operative chemoradiotherapy with post-operative chemotherapy. They found that the addition of chemotherapy to preoperative radiotherapy resulted in significant improvement in local control despite no improvements in overall survival. The strongest local control at 5 years (7.6%) was observed in the group who received preoperative chemoradiotherapy and postoperative chemotherapy [21].

Chemoradiation

Types of Chemotherapy

Fluoropyridimidines have been used for their role as radiation sensitizing agents and are the standard chemotherapeutic agents used in neoadjuvant chemoradiotherapy (NACRT). Classically, infusional 5-fluorouracil (5-FU) +/− Leucovorin (folinic acid) has been the chemotherapy of choice in NACRT. 5-FU can be delivered as an interrupted bolus infusion or protracted venous infusion (PVI), concurrently with pelvic radiation. The US GI Intergroup 86-47-51 trial compared bolus 5-FU with PVI 5-FU showing the latter to be associated with improved 4-year DFS (53 vs. 63%; $p = 0.01$) and 4-year overall survival (60 vs. 70%; $p = 0.005$), at least partly due to reduced distant recurrences [22]. However, PVI chemotherapy requires central venous access and patient compliance and is known to be associated with an increased severity of diarrhea [23].

Capecitabine is an oral prodrug converted to 5-FU by intracellular thymidine phosphorylase and has been shown to be non-inferior to infusional 5-FU with a favorable adverse reaction profile in the setting of NACRT [24–26]. This non-inferiority of capecitabine was shown in a

German phase III randomized controlled trial where stage II and III rectal cancer patients were randomized to either capecitabine or 5-FU radiosensitizing chemotherapy with radiation, in the pre- or post-operative setting. This trial demonstrated Capecitabine to be non-inferior to 5-FU in 5-year overall survival (76% vs. 67%; p = 0.004) with a post-hoc test for superiority in favour of capecitabine (p = 0.05). 3-year Disease-free survival was 75% with capecitabine versus 67% with 5-FU (p = 0.07). There was no significant difference in local recurrences although there was a significantly lower rate of systemic recurrences with capecitabine [26]. In the NSAPB-R04 study, authors compared capecitabine, with or without oxaliplatin, to infusional 5-FU with or without oxaliplatin, as the neoadjuvant chemoradiation regimen for patients with stage II and III rectal cancer. When comparing oral capecitabine with infusional 5-FU groups, no differences were noted in sphincter preservation, complete pathological responsiveness, or rates of down-staging [24, 27].

Given the benefits of Oxaliplatin addition to 5-FU in the adjuvant treatment of locally advanced colon and rectal cancer (see Adjuvant Therapy section), various large prospective trials have investigated its utility in the setting of NACRT. The NSABP R-04, the STAR-01, the ACCORD 12/0405-Prodige 2, and the PETACC-6 trials all investigated the addition of this agent to 5-FU based NACRT. These studies failed to show any significant improvements in pathologic complete response, locoregional control, and survival outcomes associated with the addition of oxaliplatin. There was, however, an increase in grade 3–4 toxicity in the oxaliplatin groups in these studies [24, 28–30]. The German CAO/ARO/AIO-04 trial was the only study that showed higher pathological complete response (pCR) (17% vs 13%; p = 0.038) and 3-year DFS (75.9% vs 71.2%; p = 0.03) without increased overall toxicity in the Oxaliplatin group [31, 32]. It should be noted that this study has been criticized for the inclusion of Oxaliplatin in the adjuvant setting as well as using different 5-FU dosing regimens for the two arms [6]. The findings of these trials suggest that the addition of oxaliplatin to NACRT is currently not warranted given the increased associated toxicity with minimal survival benefit.

Lastly, initial results of the Chinese FOWARC multicenter, randomized phase III trial have shown that the use of modified FOLFOX6 (mFOLFOX6) chemotherapy concurrent with radiotherapy preoperatively may result in increased rates of down-staging with acceptable tolerability. In this study, patients with LARC were randomized to one of three groups: (1) fluorouracil-radiotherapy (5-FU with radiotherapy, followed by surgery and adjuvant 5-FU), (2) mFOLFOX6-radiotherapy [similar to the previous group with intravenous Oxaliplatin 85 mg/m^2 on day 1 of each cycle (modified FOLFOX6)], and (3) mFOLFOX6 (four to six cycles of mFOLFOX6 followed by surgery and six to eight cycles of mFOLFOX6). The mFOLFOX6-radiotherapy group had higher rates of pCR (14.0% vs 27.5%) compared with fluorouracil-radiotherapy group. Although there were increased grade 3–4 toxicity rates in the mFOLFOX6 group, the compliance was unchanged [33]. These findings suggest that NACRT with mFOLFOX6 may potentially result in improved outcomes given the observed increased pCR; however, this preliminary finding requires further confirmation. Additionally, the authors are expecting the final primary outcome, DFS, to be available in 2017, which may provide more robust evidence for this new neoadjuvant regimen. Until then, 5-FU/capecitabine based NACRT without oxaliplatin remains standard of care.

Types of Radiation Therapy

Currently, there are two common variations to delivering radiation therapy (RT) preoperatively. The efficacy of these forms of radiation stem from multiple sources of evidence, but one must be selective for those that were performed in the era of the TME approach to proctectomy. Short-course radiation therapy (SCRT), which is mostly endorsed in Europe, involves 5 Gy fractions of radiation over 5 days for a total of 25 Gy followed by surgery in 1 week. One of the seminal studies to investigate this was the Dutch TME trial. In this trial patients were randomized to short course radiation therapy before or after TME surgery. Local recurrence was found to be

significantly lower in the neoadjuvant radiation therapy group (4.6 vs. 11%; p < 0.0001) with similar 10-year distant recurrence (25 vs. 28%; p = 0.21) or overall survival (48 vs. 49%; p = 0.86) [10, 34].

The alternative approach, long-course chemoradiation therapy (CRT), is generally the standard regimen used in North America and involves 1.8–2.0 Gy radiation per day over 20–25 fractions for 5–6 weeks for a total of 45–50 Gy. This regimen is traditionally followed by surgery in 6–8 weeks, although this period has been gradually increasing as we will discuss further in an upcoming section. This regimen is often combined with radiosensitizing fluoropyrimidine-based chemotherapy. One of the original studies to demonstrate the effect of this form of neoadjuvant therapy was the German Rectal Cancer Trial. This landmark trial randomized patients with stage II and III rectal cancer to receive preoperative and postoperative chemoradiation in addition to 5FU-based adjuvant chemotherapy. They showed a significant reduction in local recurrence rates when CRT was given in the neoadjuvant setting (6% vs 13%; p = 0.006), which also persisted on the 10-year follow-up assessment. Chemotherapy associated toxicity was also lower in the neoadjuvant group (27 vs. 40 %; p = 0.01). However, overall survival and rates of distant metastasis (36%) did not change significantly between the two groups [35].

It is thought that, in addition to lower costs, SCRT would result in lower rates of early toxicity with a chance for delayed toxicity [13, 35–37]. Conversely, there is evidence that CRT could result in greater downstaging when delivered in the neoadjuvant setting. Two randomized controlled trials have investigated the potential benefits of one regimen over the other [38, 39]. The Polish Colorectal Study Group randomized 316 patients to receive either SCRT or CRT. The authors found no significant differences in rates of local recurrence (9 vs. 14.2%; p = 0.17), disease-free survival (58.4 vs. 55.6%; p = 0.82), or overall survival (67.2 vs. 66.2%; p = 0.96) when comparing the SCRT with CRT, respectively [38]. However, patients in the CRT group had higher pCR rates (16% vs. 1%) and lower incidences of involved circumferential resection margin (4% vs. 13%; p = 0.017) with no differences in sphincter preservation (58 vs. 61%; p = 0.57). Despite increased acute toxicity in the CRT group (18.2 vs 3.2%; p < 0.001) the rates of post-operative complications were similar [38].

In a similar trial by the Tran-Tasman Radiation Oncology Group (TROG-01.04), Ngan et al. [39] randomized 326 patients to SCRT or CRT followed by surgery and 6 months of adjuvant chemotherapy. The authors reported no significant differences in overall survival, distant recurrence or late toxicity between the two groups. Although there was a trend toward lower cumulative local recurrence at 3 years (4.4% vs. 7.5%) and 5 years (5.7% vs. 7.5%) in the CRT arm, these findings were not statistically significant [39].

Zhou et al. [40] recently published a meta-analysis of the existing studies comparing neoadjuvant SCRT with CRT and confirmed no significant difference in local recurrence, disease-free or overall survival between the two modalities. There was an increased rate of pCR (RR 0.15; p = 0.003) at the cost of having increased grade 3-4 toxicity in the CRT group (RR: 0.13; p < 0.00001). Of note, the long-term toxic effects were not substantially different between SCRT and CRT. Given the results of these studies, currently either SCRT or CRT is appropriate in the neoadjuvant setting as represented by the different European and North American Guidelines.

The Stockholm Colorectal Cancer Study Group initiated the multicenter randomized Stockholm III Trial, to further study the outcomes related to various RT fractionation regimens and timing to surgery for rectal cancer, with local recurrence as the primary endpoint [41]. The three preoperative RT regimens included short-course RT (5 × 5 Gy) and surgery within 1week (group 1), short-course RT and surgery after 4–8 weeks (group 2), and long-course RT (25 × 2Gy) and surgery after 4–8 weeks (group 3). The first interim analysis focused on feasibility, compliance and complications after RT and surgery, and found no significant difference in postoperative complications between the three groups (46.6%, 40.0%, and 32% in groups 1, 2, and 3, respectively; p = 0.164) [41]. The second interim analysis compared the pathological outcomes of delaying surgery in the

two short-course RT arms (groups 1 and 2), and demonstrated earlier ypT categories, higher pCR rates (11.8% vs. 1.7%; p = 0.001) and Dworak grade 4 tumor regression (10.1% vs 1.7%; p < 0.001) in group 2 compared with group 1 [42].

A novel approach for delivery of neoadjuvant RT is the consideration of selective use of RT. With recent evidence supporting potential benefits of neoadjuvant systemic chemotherapy (see *induction chemotherapy* section), the phase II/III PROSPECT trial (NCT01515787) is currently underway comparing neoadjuvant FOLFOX with selective use of chemoradiation to standard neoadjuvant CRT [23]. In this study, patients with LARC are randomized to two groups. The first group will undergo standard neoadjuvant chemoradiation therapy (5-FU or Capecitabine with RT), followed by surgery and adjuvant chemotherapy. In the second group, after 6 cycles of neoadjuvant FOLFOX, tumor response is measured by MRI or endorectal ultrasound (ERUS). If the tumor has not regressed by at least 20%, patients will undergo the standard CRT used in group 1. However, those with >20% tumor response will go on to surgical resection followed by adjuvant therapy [43].

Intraoperative Radiation Therapy

As previously discussed, radiotherapy, with or without chemotherapy, is currently used in the neoadjuvant setting to improve local recurrence and to potentially down-size tumors and facilitate an R0 surgical resection. However, normal tissue tolerance limits the dose of radiotherapy preoperatively [44]. Therefore, the concept of intraoperative radiotherapy (IORT) with either electrons (IOERT) or high dose brachytherapy (HDR-IORT), especially in cases of LARC, borderline resectable T4 rectal cancers, has been introduced as part of the multimodality treatment of LARC [45]. IORT allows for a targeted boost delivery comparable to an additional 30–40 Gy of fractionated irradiation with the possibility to shield or remove dose-sensitive surrounding structures [46].

Studies to date have shown mixed results in terms of the benefits of IORT on oncologic outcomes. As an example, two RCT's have failed to show a benefit to the addition of IORT to the treatment of LARC [47–49]. Conversely, a study by Kusters et al. [46] showed no local recurrences in 55% of patients treated with IORT for positive resection margins. In another study by Ferenschild et al. [50], the addition of HDR-IORT resulted in improved 5-year local control in patients where R0 resection was not feasible (58% vs 0%). Lastly, in a series by Valentini et al. [51], the authors demonstrated an improved 5-year local control rate in patients with T4 rectal cancer who received IORT following standard preoperative chemoradiation and an R0 resection (100% vs 81%; p = 0.014).

In summary, the results of these studies support the effect of IORT on residual tumor cells that may result in improved local control of locally advanced rectal cancers, in particular, margin positive or margin close T4 lesions.

Endoluminal Brachytherapy

High-dose rate endorectal brachytherapy (HDREBT) has been used in the preoperative setting to down-size tumors and facilitate sphincter preservation surgery, especially in low rectal cancers [52]. Kusunoki et al. [53] was the first to report improved local control with the use of endorectal brachytherapy prior to sphincter-preserving surgery. Patients who underwent brachytherapy and surgery had a lower cumulative 5-year local recurrence rate compared to those undergoing surgery alone (11% vs. 38%; p = 0.004) [53]. Aside from its role as monotherapy, HDREBT has also been successfully used as an adjunct to neoadjuvant external beam RT. Applet et al. [54] randomized 248 with non-metastatic LARC to chemoradiation with or without brachytherapy boost followed by surgical resection 8 weeks later. In the brachytherapy boost group, the authors found significant improvements in R0 resection rates and near 50% increase in tumor response for cT3 tumors, with no increase in surgical complications or early toxicity. There were no differences in progression free or overall survival between the two arms.

Lastly, given the lack of nodal drainage and mesorectal fascia coverage in HDREBT and potential added benefit of nodal sterilization by external beam radiation, a group from John Hopkins is comparing neoadjuvant external beam radiation to HDREBT in a phase III trial [52].

Currently, other studies are also analyzing the role of HDREBT in the radical treatment of early rectal cancer [52].

Timing of Surgery Post-Chemoradiation

The optimal timing of surgery after radiotherapy remains a topic of much debate. The rational for delaying surgery post radiation is to maximize the effects of RT on tumor cell death [55]. However, delay in surgery may also result in increased fibrosis and potentially a more challenging operation. In addition, theoretically the benefits of neoadjuvant therapy may wane with time.

One of the seminal randomized controlled trials to investigate this topic is the Lyon R90-01 trial. In this study, the authors randomized 201 patients to operation either 2 weeks or 6–8 weeks after radiation. They found significant improvements in clinical tumor response (53.1 vs. 71.1%; $p = 0.007$) and pathological tumor downstaging (10.3 vs. 26%; $p = 0.005$) when operation was performed 6 to 8 weeks after radiation. There were, however, no significant differences in sphincter preserving surgery, morbidity, local recurrence or short-term survival between the two groups [56]. Similarly, other studies by Tulchinsky et al. [57] and Kalady et al. [58] showed the only independent factor associated with good response or pCR was longer delay between radiation and surgery (7 weeks or longer). A recent meta-analysis of 13 retrospective studies also confirmed these findings [59].

To further study the relationship between a longer interval after neoadjuvant chemoradiation (nCRT-surgery interval) and pCR, Probst and colleagues [60] reviewed 17,255 patients from the National Cancer Database. The authors divided patients into various nCRT-surgery intervals of >8 weeks, 6–8 weeks, and <6 weeks and demonstrated pCR rates of 13.2%, 11.7%, and 8.7%, respectively for each group ($p < 0.001$). Higher odds of pCR (OR = 1.12, 95% CI = 1.01–1.25) and tumor downstaging (OR = 1.11, 95% CI = 1.02–1.25) were noted in the nCRT-surgery interval >8 weeks. Lastly, the cumulative pCR rate appeared to reach a maximum between weeks 10 and 11.

Most recently, the French GRECCAR-6 randomized trial compared the effect of delay of 7 weeks with 11 weeks from CRT to time of surgery on the pCR rate as the primary outcome of the study. They found that this 4-week increase in delay not only resulted in similar pCR but was also associated with increased post-operative morbidity and worse quality of mesorectal excision. The authors concluded that surgery after 11 weeks from time of CRT should be avoided, especially without the use of chemotherapy in the interim [61]. Additionally, a study from Royal Marsden Hospital in the United Kingdom is currently randomizing patients to surgery 6 weeks versus 12 weeks after neoadjuvant radiotherapy/chemoradiation. The primary end-point of this study is to measure the difference in the proportion of patients in each arm, down-staged according to the T stage. The results are pending at this time (clinicaltrials.gov ID: NCT01037049).

As can be seen from the available evidence, there appears to be a favorable impact on pCR by delaying the time interval from radiation to surgery; however, the most optimal waiting period is still to be determined, although 8-10 weeks is a reasonable period until further information is available.

Surgery Related Outcomes Post Chemoradiation

Although mostly as a secondary outcome, many studies have investigated the role of neoadjuvant therapy on various surgical outcomes including sphincter preservation (SP), anastomotic integrity and various functional outcomes after surgery.

For the most part, if feasible and oncologically safe, patients prefer sphincter-preserving procedures compared to radical abdominoperineal resection (APR). Due to improvements in surgical technique and concepts, changes in neoadjuvant treatment, as well as availability of specialty centers in rectal surgery, SP rates as high 77% have been achieved [62]. Lyon R90-01 study looked at SP as a secondary outcome when comparing 2 weeks versus a 6–8 week delay after completion of radiotherapy. The authors did not

find a significant difference in rates of SP between the two groups [56]. The Polish as well as several other trials have also failed to show any increase in SP rates in patients treated with neoadjuvant SCRT versus CRT, despite improved pCR rates with the latter [63–65].

Anastomotic leak (AL) is one of the most feared surgical complications in the treatment of rectal cancer. To date, there has been insufficient data on the relationship between neoadjuvant chemoradiation and AL. Most studies are either observational or insufficiently powered sine they include AL as a secondary outcome [66]. Although some small observational studies have suggested an increase AL associated with NACRT [67–69], a recent meta-analysis of 7 RCT's by Qin et al. [70] found that NACRT was not an independent risk factor for AL (OR 1.02; 95% CI: 0.80–1.30; p = 0.88). As it stands, there is insufficient data to show any strong association between NACRT and AL.

In addition to SP and AL, the effect of neoadjuvant treatment on various functional outcomes such as sexual dysfunction and urinary or fecal incontinence has also been investigated. A follow up of the Dutch trial investigating functional outcomes after neoadjuvant radiotherapy showed that radiated patients have significantly higher rates of daytime and night incontinence, anal mucus and blood loss, and daily pad use [71]. In a report of a multicenter randomized trial, Marijnen et al. [72] found preoperative radiotherapy to be associated with higher rates of sexual dysfunction. However, in a follow-up study from the MRC CR07/NCIC-CTG C016 trial, the authors found that surgery, and not radiotherapy, was the principally associated cause [73]. Lastly, a comprehensive meta-analysis of observational and prospective trials by Loos et al. [74] demonstrated an increased rate of stool incontinence in irradiated patients (RR 1.67; p < 0.00001). However, the authors did not find an increased incidence of sexual dysfunction in the irradiated group.

Toxicity and Compliance

In addition to tumor downstaging and the theorized increased effect on well-oxygenated tissue, one of the main benefits to neoadjuvant treatment (compared to adjuvant) is improved patient tolerance to the therapeutic regimen [75, 76]. Many studies have compared the toxicity of SCRT vs. CRT radiation regimens with inconsistent results. In 2014, Zhou et al. [40] performed a meta-analysis of 6 trials to investigate rates of grade 3–4 toxicity in patients undergoing neoadjuvant therapy. They reported a significantly lower rate of acute toxicity in the SCRT group (RR 0.13; 95% CI 0.06–0.28; p < 0.00001). This increase in grade 3–4 toxicity with CRT was also confirmed in a recent Cochrane review by De Caluwe et al. [77] (OR: 1.68–10; p < 0.002). The EORTC trial also investigated toxicity and adherence related to various pre- and post-operative treatments and demonstrated an adherence rate of 98% compared to 95.5% when comparing radiotherapy with combination chemoradiation therapy [21]. In the same study, authors also demonstrated a higher adherence rate to 5-FU infusion in the neoadjuvant setting compared to adjuvant (82% vs. 42.9%).

Nevertheless, it is now established that compliance to treatment is improved with neoadjuvant treatment compared to adjuvant. This may be the result of patients being more physically and mentally fit at the time of therapy delivery pre-operatively. For this reason, studies are now investigating the role of pre-habilitation programs peri-operatively to improve patient outcomes and adherence to treatment [78, 79].

Pathologic Complete Response and the "Watch and Wait" Approach

Approximately 15–27% of patients with LARC achieve pCR (ypT0N0) after neoadjuvant chemotherapy [80]. These responders are known to have better oncological outcomes such as local recurrence rates below 1% and 5-year survival rates greater than 95% [80, 81]. Given the excellent prognosis of this patient population and potential costs and morbidities associated with surgery, studies are now investigating the role of non-operative management (NOM) or "watch and wait" approaches in patients achieving a complete clinical response (cCR) post NACRT. The largest experience with this

approach comes from Brazil where Habr-Gama and colleagues [82] followed patients with evidence of a cCR post-neoadjuvant therapy clinically and radiologically using an intense form of surveillance. Patients underwent a TME if there was evidence of tumor persistence after neoadjuvant therapy or a local regrowth in the surveillance period. They achieved an overall rate of 78% organ preservation with 91% overall survival in the NOM group. There was a 10% local regrowth rate in the NOM group during follow-up; however, all patients underwent curative salvage surgery. Lastly, the oncological outcomes of the patients with cCR in the NOM group were similar to those with pCR after TME [82–85]. Similar promising results for NOM after cCR have been reported from Maastricht University in the Netherlands as well as Memorial Sloan Kettering Cancer Centre (MSKCC) in the United States [85, 86], among others.

In summary, these preliminary results demonstrate a potential role for NOM in a highly select group of patients who achieve cCR after neoadjuvant therapy. However, at this stage, such patients must be surveilled very closely in highly specialized cancer centers to be able to detect potential local recurrences early and treat them accordingly. Another limitation of this approach is the discordance between cCR and pCR and challenges with differentiating tumor from fibrosis on imaging after neoadjuvant treatment. Therefore, standardization of the clinical and endoscopic features to determine cCR is of utmost importance for this approach to be a reliable [13].

Adjuvant Therapy

Adjuvant Chemotherapy

The advent of modern surgical techniques combined with NACRT has resulted in improved locoregional control; however, distant relapse remains a significant issue [6].

In 1990, the landmark study by Moertel et al. [87] showed a 41% reduction in cancer recurrence and 33% reduction in death of patients with stage III colon cancer undergoing adjuvant chemotherapy (aCT) compared to observation alone after surgery. Additionally, a 2012 Cochrane review of 21 randomized control trials further showed a significant risk reduction in mortality of up to 17% in curatively treated rectal cancer patients undergoing adjuvant chemotherapy compared to post-operative observation. However, in 20 of these studies, patients did not receive neoadjuvant therapy preoperatively [88]. Lastly, a meta-analysis by Biagi et al. [89] showed a 14% increase in mortality for every 4 weeks of delay in aCT following the first 4 weeks after colorectal cancer surgery. The results of such studies combined with the extrapolation of data from colon cancer treatment have resulted in the routine use of aCT in LARC.

Given the lack of Level I evidence, there remains a great deal of controversy in the role of aCT post neoadjuvant therapy in reducing distant recurrences or improving survival in LARC. This is evident by varying treatment guidelines across the globe; for instance, per 2015 National Comprehensive Cancer Network (NCCN) guidelines, all patients who receive preoperative CRT should receive aCT regardless of pathological stage [90]. Although not standard practice in the Netherlands or Norway, the European Society for Medical Oncology (ESMO) recommends aCT in pathological stage III and “high-risk” stage II rectal cancers. Lastly, the 2012 European consensus conference on colorectal cancer did not reach a consensus for use of aCT in stage II or III disease [8, 91, 92].

In a recent review by Netter et al. [11], existing evidence addressing the role of aCT in LARC patients after neoadjuvant CRT was reviewed. Four randomized phase III trials recently compared the survival outcomes of aCT with observation and have failed to show any statistical efficacy for 5FU based aCT. The European Organization for Research and Treatment of Cancer Trial (EORTC 22921) randomized 1011 patients with LARC into 4 therapeutic groups: neoadjuvant radiotherapy or CRT followed by three months of aCT with FUFOL (5FU and Leucovorin) or observation only. There was no significant improvement in 10-year OS (51.8 vs. 48.4%, HR: 0.91, 95% CI: 0.77–1.09; p = 0.32) or DFS (47 vs. 43.7%, HR: 0.91, 95% CI: 0.77–

1.08; p = 0.29) [93]. The CHRONICLE Trial randomized 113 patients with LARC receiving preoperative 5FU CRT to post-operative 6 cycles of XELOX (capecitabine and oxaliplatin) or observation alone. This study too, failed to show a significant difference in 3-year DFS between the two groups (78 vs. 71%, HR: 0.80, 95% CI: 0.38–1.69; p = 0.56) [94, 95]. The PROCTOR-SCRIPT Trial compared observation with 5FU-based aCT in 437 patients receiving neoadjuvant radiation (86%) or CRT (14%). There was no significant difference in 5-year OS (80.4 vs. 79.2%, HR: 0.93, 95% CI: 0.62–1.39; p = 0.73) or DFS (62.7 vs. 55.4%, HR: 0.80, 95% CI: 0.60–1.07; p = 0.13) in this study either [96]. Lastly, the Italian trial, I-CNR-RT randomized 634 patients with LARC to 6 cycles of adjuvant 5FU/leucovorin or observation. The authors showed similar 5-year OS (69.1 vs. 70%, HR: 1.045, 95% CI: 0.775–1.410; p = 0.772) and DFS (65.3 vs. 62.8%, HR: 0.997, 95% CI: 0.724–1.319; p = 0.882) between the two arms [97]. Although none of these four RCT's showed any survival benefit for 5FU-based aCT, their results should be interpreted with caution because of limitations such as heterogeneity of the inclusion criteria between studies, lack of statistical power, poor adherence and variations in preoperative, operative and adjuvant regimens [11].

Three meta-analyses have also looked at the role of aCT post neoadjuvant treatment and surgery in patients with LARC. Breugom et al. [96] performed a meta-analysis of the aforementioned four RCT's (EORTC, CHRONICLE, PROCTOR-SCRIPT, I-CNR-RT,) including 1196 patients with ypTNM stage II and III and R0 resection. No improvement in 5-year OS, DFS or distant recurrences was observed. Conversely, the meta-analysis of 16 studies by Petrelli et al. [98] did show an improvement in 5-year OS (HR: 0.64, 95% CI: 0.46–0.88; p = 0.006) and DFS (HR: 0.71, 95% CI: 0.6–0.83; p < 0.0001) in patients treated with 5FU-based aCT; however, this survival benefit was more significant in retrospective studies analyzed. Lastly, Bujko et al. [99] in 2015 included 5 studies (EORTC, I-CNR-RT, PROCTOR-SCRIPT, QUASAR, CHRONICLE) as the first part of their meta-analysis and reached the same conclusion of no significant benefit with aCT on OS (HR: 0.95, 95% CI: 0.82–1.10; p = 0.49) or DFS (HR: 0.92, 95% CI: 0.80–1.04; p = 0.19). There was, however, an improvement in DFS only in patients with stage II and III disease after subgroup analyses (HR: 0.79, 95% CI: 0.62–1.00; p = 0.047).

Currently the combination of 5FU/leucovorin or capecitabine (an orally delivered prodrug formulation of 5-FU) with oxaliplatin (FOLFOX or XELOX, respectively) is the standard treatment for locally advanced colon cancer in the adjuvant setting (201). The evidence for this regimen came from the Multicenter International Study of oxaliplatin/(5-FU)/leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial which found addition of oxaliplatin to 5FU-based aCT improved 5-year DFS survival in stage II and III colon cancer (73.3 vs. 67.4%; p = 0.03) and 6-year OS in stage III colon cancer (72.9 vs. 68.7%; p = 0.023), when compared with 5FU alone [100]. The survival benefit of oxaliplatin addition to 5FU-based aCT in stage II and III colon cancer was further supported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 in 2011 where a significant improvement in the 5year-DFS of the patients receiving combination therapy was observed (69.4 vs. 64.2%; p = 0.002) [101].

Extrapolating from colon cancer data, it seems logical that the addition of oxaliplatin to 5FU-based aCT in LARC would improve its efficacy. Two randomized trials have attempted to address this issue. The ADORE phase II Korean trial randomized 321 patients with LARC after neoadjuvant CRT and TME surgery to either receive mFOLFOX or 5FU/leucovorin. They showed an improved 3-year DFS in the FOLFOX group despite increased but acceptable, mostly grade 1–2, toxicity (72 vs. 63%, HR: 0.66, 95% CI: 0.43–0.99; p = 0.047). Subgroup analysis in this trial showed the 3-year DFS to be mainly attributable to stage III cancers [102]. Unlike previously, the adherence rates in both trials were fair (96% patients in ADORE trial and 82%) patients in CAO/ARO/AIO-04 completed aCT. In the phase III German trial of CAO/ARO/AIO-04, 1265 patients with LARC were randomized to receive 5FU with oxaliplatin (mFOLFOX) or 5FU bolus only

(without leucovorin) as neoadjuvant CRT and aCT (4 months). This trial, too, showed a significant improvement in 3-year DFS with the addition of oxaliplatin (75.9% vs. 71.2% HR: 0.79, 95% CI: 0.64–0.98; $p = 0.03$) [103]. Although both trials used a rather suboptimal 5FU regimen, they do provide support for the use of combination therapy with oxaliplatin as the chemotherapy regimen of choice with acceptable toxicities in at least stage III and high-risk stage II rectal cancers.

Induction vs. Adjuvant Chemotherapy

The current 'gold standard' treatment for LARC in the United States is neoadjuvant CRT, followed by TME resection and adjuvant chemotherapy (aCT). However, given the unchanged distant recurrence rate of 30% despite advances in operative and adjuvant therapies and difficulties with adherence to postoperative aCT, there is now interest in delivery of systemic chemotherapy preoperatively as induction chemotherapy (iCT) also known as total neoadjuvant therapy [33]. This strategy would theoretically improve distant metastasis control and potentially enhance survival by improving compliance as well as treating occult micro-metastases early in the treatment of LARC [104]. Additionally, iCT could potentially contribute to preoperative downstaging of the tumor which is known to be associated with a higher likelihood of R0 resection and a lower chance of local recurrence [33].

Chau et al. [105] from Royal Marsden Hospital, investigated the effect of neoadjuvant capecitabine/oxaliplatin before CRT and TME in patients with high-risk rectal cancer. Seventy-seven patients in the study received 12 weeks of neoadjuvant capecitabine/oxaliplatin followed by CRT, TME and additional 12 weeks of Capecitabine. Authors showed substantial tumor regression (97% after CRT) and symptomatic response rates (86%), and 99% R0 resection with a 24% pCR rate [105].

To follow-up on Royal Marsden Hospital findings, a phase II trial in Spain randomized 108 patients with LARC to either preoperative CRT, TME resection and 4 cycles of adjuvant capecitabine and oxaliplatin (CaPOX) or induction CaPOX followed by CRT and TME resection. They did not show any significant difference in pCR, downstaging, tumor regression or R0 resection rates. They did however find lower grade 3–4 toxicity (19% vs. 54%) and better compliance in the induction arm [106].

The role of iCT after CRT in the neoadjuvant setting for LARC has also been studied in the TIMING trial (NCT00335816; Timing of Rectal Cancer Response to Chemoradiotherapy Trial). They demonstrated that delivering two, four, or six cycles of FOLFOX after CRT increased the pCR rates up to 25%, 30%, and 38%, respectively, compared with CRT alone (18%). There was no significant increase in surgical complications or adverse events and 80% completed consolidation CT without interruption [107, 108].

As reflected in the updated NCCN guidelines, despite the lack of data from large scale prospective trials, the results of these studies show that iCT (FOLFOX or CAPOX) before CRT may be considered as an acceptable alternative in the treatment of LARC [7, 23].

Lastly, given the promising results of iCT, studies are currently investigating the feasibility of the selective use of CRT in the context of iCT. In particular, the PROSPECT study (NCT01515787) is a randomized trial comparing neoadjuvant FOLFOX with selective use of CRT (e.g. if intolerant to chemotherapy or progression of disease on chemotherapy) to standard neoadjuvant chemoradiation for patients eligible for TME surgery based on the location of tumor [23].

Adjuvant Chemotherapy Following PCR

The current recommendations from the NCCN guidelines encourage 6 months of total peri-operative 5-FU-based chemotherapy, with approximately 4.5 months of the therapy occurring in the adjuvant setting [7]. However, in attempts to further individualize care and reduce unnecessary

toxicity in the treatment of patients with LARC, multiple studies have looked at the possibility of withholding adjuvant chemotherapy in patients who achieve pCR after CRT.

Approximately 15–27% of patients with LARC undergoing CRT achieve pCR [109]. These patients with pCR are thought to have improved oncological outcomes when compared with non-responders. A literature review in 2010 by Maas et al. [80] found pCR to be associated with improved 5-year DFS (83.3 vs. 65.6%), lower local recurrence rates (2.8 vs. 9.7%), improved distant metastasis-free survival (88.8 vs. 74.9%), and improved overall survival (87.6 vs. 76.4%). Therefore, it is logical to consider foregoing aCT in this patient population with already good prognosis in hopes of reducing chemotherapy related costs and toxicities.

One of the main studies investigating this issue specifically has been an observational study published by García-Albéniz [110]. In this study, patients with cT3-T4 underwent CRT followed by TME surgery. Subsequently, patients with pCR (15%) did not receive aCT whereas others received 5FU-based aCT on an individual basis. After a median follow up of 58.3 months, the DFS (96%) and OS (100%) were analyzed. Only one patient out of 26 in the pCR group had distant recurrence at 15 months with no local recurrence. In comparison with an external cohort of patients with LARC receiving NACT and TME surgery followed by aCT, there was no significant benefit in the local recurrence, distant metastasis, overall survival, or disease-free survival rates.

Additionally, a recent propensity matched cohort of the National Cancer Database was completed comparing the oncologic outcomes of LARC patients treated with neoadjuvant chemoradiotherapy with a pCR. In this study, Dossa and colleagues matched 667 patients, in whom over a median follow up of 3.1 years, there was an improved overall survival in pCR patients who had receieved adjuvant therapy (hazard ratio, 0.44; 95% CI, 0.28–0.70). Furthermore, a stratified analysis suggested that the effect was only preent in patients with a positive pretreatment nodal status (hazard ratio, 0.24; 95% CI, 0.10–0.58) [111].

In an era in which the need for aCT is controversial, the role of this adjuvant modality in a subset of patients with an already improved prognosis needs to be reconsidered to reduce the associated costs and unnecessary toxicity [112, 113].

Toxicity and Compliance

Despite current recommendations by NCCN for adjuvant chemotherapy, the compliance rate appears to be low. A recent National Data Base analysis by Xu et al. [114] evaluated the compliance rate to the current NCCN guidelines for locally advanced rectal cancer recommending completion of adjuvant chemotherapy. They found an alarmingly low compliance rate of 32% among patients eligible to receive adjuvant chemotherapy. The previously mentioned clinical trials showing no survival benefit with the addition of aCT after neoadjuvant CRT and TME surgery in LARC also highlighted the issue of poor adherence to aCT. The compliance rates for EORTC, CHRONICLE and PROCTOR/SCRIPT trial were 43%, 48.1% and 73.6%, respectively [21, 96, 113].

Many system and patient factors have been identified to play a role in poor adherence to aCT. Age, gender, race, number of medical comorbidities, pathological complete response, stage and pathology, and type of hospital were all found to be associated with compliance by Xu et al. [114] in their analysis of the National Cancer Data Base.

Adjuvant Radiotherapy

Preoperative radiation has been shown to be superior to postoperative radiation in terms of local recurrence benefits and functional outcomes [6] and thus is the standard of care for LARC. This is based on two large studies, namely the Dutch TME trial and German CAO/

ARO/ AIO-94 phase III trial [10, 34]. As an example, in the Dutch trial patients were randomized to radiation therapy before or after TME surgery. Local recurrence was found to be significantly lower in the radiation therapy group (4.6 vs. 11%; $p < 0.0001$) with similar 10-year distant recurrence (25 vs. 28%; $p = 0.21$) or overall survival (48 vs. 49%; $p = 0.86$) [10, 34].

Chemoradiation

North Central Cancer Treatment Group (NCCTG 794751) trial was the first trial to provide support for improved local recurrence and survival in patients receiving adjuvant chemoradation [115]. The benefit of adjuvant chemoradiation was further supported by the Norwegian Adjuvant Rectal Cancer Project Group in 1997 where they randomized patients to adjuvant chemoradation (5FU-bolus with external beam radiation therapy) or surgery alone. No form of maintenance chemotherapy was used in this trial. The authors found a significant improvement in local recurrence (12% vs. 30%) and overall survival (64% vs. 50%) in the chemotherapy group compared with surgery alone group [116].

Subsequently, to further improve local recurrence and ease of operation by downstaging the tumor upfront as well preventing other downsides to adjuvant chemoradiation such as small bowel and anastomotic irradiation, attempts were made to deliver chemoradation preoperatively as a neoadjuvant treatment [75].

In 2004, results published from the German Trial solidified the superiority of chemoradiation therapy as a neoadjuvant modality as compared to the adjuvant setting. This landmark trial randomized patients with stage II and III rectal cancer to receive preoperative and postoperative chemoradiation in addition to 5FU-based adjuvant chemotherapy. They showed a significant reduction in local recurrence rates when CRT was given in the neoadjuvant setting (6% vs 13%; $p = 0.006$). Chemotherapy associated toxicity was also lower in the neoadjuvant group (27 vs. 40%; $p = 0.01$). However, overall survival and rates of distant metastasis (36%) did not significantly change between the two groups. Based on these results and others, as well as the improvement in local control, the use of CRT in the neoadjuvant setting is currently the recommended regimen [35].

Roles of Adjuvant Therapy in Metastatic and Recurrent Rectal Cancers

Metastatic (Stage IV) Rectal Cancer

Approximately 25% of colorectal cancer cases have metastases at the time of diagnosis, with liver presenting as the most common site for CRC metastasis. Patients with isolated liver metastases who are surgical candidates should be offered resection as this will offer them the greatest likelihood of cure. The median OS of untreated patients in this setting is less than 1 year [117] whereas those who have hepatic resection could have a 5-year survival of up to 31–45% [118–120].

The majority (80–90%) of colorectal liver metastases (CRLM) are unresectable at first presentation [121]; however, with chemotherapy these patients can be converted to having resectable disease and a comparable postoperative survival to initially unresectable CRLM ("conversion chemotherapy") [122, 123]. Additionally, systemic chemotherapy may not only alleviate symptoms but is also associated with improved disease control and survival [124]. The most commonly used components for systemic chemotherapy in metastatic CRC (mCRC) include fluoropyrimidines [intravenous 5-fluorouracil (5-FU) and oral Capecitabine], irinotecan, and Oxaliplatin [125]. FOLFOX (bolus and infusional 5-FU/LV plus Oxaliplatin), CapeOX (oral Capecitabine plus Oxaliplatin), and FOLFIRI [bolus and infusional 5-FU/leucovorin (LV) plus irinotecan] are the most common regimens used in mCRC [125].

The addition of biologic agents to target angiogenesis (e.g., bevacizumab, ramucirumab,

aflibercept and regorafenib) or the epidermal growth factor receptor (EGFR; e.g., panitumumab and cetuximab) have further resulted in improved survival in patients with mCRC [125]. Although the addition of bevacizumab has been shown to suit any cytotoxic regimen mentioned above, recent studies have shown that patients with *RAS* mutations have an inherent resistance to anti-EGFR antibody agents such as panitumumab and cetuximab [126–128]. Therefore, the use of these agents is now indicated in RAS wild type mCRC, further underlying the importance of individualized and targeted therapy.

Recurrent Rectal Cancer

Local recurrence in rectal cancer can range from 2 to 15% [35, 129, 130]. Pelvic morbidity such as pain, rectal bleeding or discharge, obstruction and sciatica may result from locally advanced primary and/or recurrent rectal cancer. To relieve symptoms, improve quality of life, and prolong survival, external beam radiotherapy (EBRT) may be used [131]. In addition to palliation in the case of inoperable tumors, radiation therapy has been used in the neoadjuvant setting to increase the chance of R0 resection rates for curative intent in recurrent rectal cancer [132]. Many of these patients, however, have received radiation therapy during their index treatment and therefore, there is concern regarding increased risk of toxicity.

Two recent systematic reviews have reported on the safety and benefit of re-irradiation in rectal cancer recurrence. Guren et al. [133] included 375 patients from retrospective and prospective studies (no RCT's were identified) who underwent (chemo)re-irradiation for either curative radical resection or palliation. Symptomatic relief in rectal bleeding and complete or partial pain relief in 83–94% of patients were observed in patients irradiated with palliative intent with median survival rate of 12–16 months. 39–89% underwent an R0 resection with a 50% recurrence and 39 to 60-month median survival. In this review, acute toxicities, mostly diarrhea and skin reactions, occurred in more than 30% of patients in earlier studies compared with 13% and 4% in later studies. The most common late toxicities were gastrointestinal and urinary complications but these were not prospectively followed consistently. Lastly authors found that hyperfractionation of chemoradiation in the case of curative treatment before surgery or once daily dosing for palliative patients to be the most appropriate regimens [133].

A more recent review by Meij et al. [134] included 474 patients who had received previous chemo(radiation) followed by surgical resection for their primary rectal cancer. All studies except one were retrospective. The authors mostly included studies utilizing re-irradiation in the form of chemoradiation for curative intent before (and some after) surgical resection of a local recurrence. Patients received either one dose of EBRT per day (n = 301) or hyperfractionated EBRT twice daily (n = 57). Grade 3–4 acute and late toxicities ranged from 0–7% and 5–16%, respectively. As expected, the most important prognostic factor was R0 resection. Overall, the authors found irradiation to be associated with improved R0 resection rates with subsequently improved local control and overall survival [134].

In summary, despite a lack of RCT's, current evidence supports the safety and benefit of re-irradiation (mostly in the form of hyperfractionated chemoradiation) in locally recurrent rectal cancer after the multimodal treatment of the primary cancer. Re-irradiation is also beneficial for palliation of recurrent rectal cancer symptoms.

Summary

The care of patients with locally advanced rectal cancer has significantly improved with the advent of various options for neoadjuvant and adjuvant therapy as well as sophisticated surgical techniques and peri-operative patient care. The rates of local recurrence in locally advanced rectal cancer are at all-time low. However, this has not translated to better survival outcomes.

Currently, studies are underway to balance the need for a survival benefit with reducing toxicity and costs associated with adjuvant therapy in rectal cancer treatment. Concepts such as induction chemotherapy, selective use of radiation therapy and the potential non-operative management of select patient groups are all indicative of efforts towards targeted, individualized care for patients with this disease. Hopefully, the introduction of the new American College of Surgeons Commission on Cancer National Accreditation Program for Rectal Cancer will result in improved use of neoadjuvant and adjuvant therapy [135].

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