The preferred integrated treatment modality for locally advanced rectal cancer is preoperative radio(chemo)therapy followed by total mesorectal excision, though certain aspects of this standard are still debated.

Worldwide, rectal cancer is a leading cause of death from cancer, affecting males and females equally.[1-3] In the United States, there were 39,870 new rectal cancer cases in 2011.[4]

Since the 1980s, the outcomes of rectal cancer have improved; both survival and disease-free intervals have increased through advances in diagnostic imaging, pathology, surgery, and integrated treatments, including radiotherapy (RT) and chemotherapy (CT). More important, the integration of these different treatment modalities has led to the modern standards for rectal cancer treatment. Here, we summarize the principal aspects of current standards for integrated treatment of locally advanced rectal cancer (LARC), comparing the European and American approaches.

Must preoperative radio(chemo)therapy be added to optimal surgery?

Surgery is the historical cornerstone of rectal cancer treatment. In the 1970s, unsatisfactory results were associated with surgery alone; local failure rates were 50% for locally advanced and node-involving presentations,[5,6] prompting attempts to increase local control and survival.

In the 1980s, adjuvant postoperative concurrent radiochemotherapy (RTCT) was evaluated in North America and was found to significantly improve survival and time to recurrence.[7,8] In 1990, the National Institutes of Health (NIH) Consensus Conference recommended postoperative integrated RTCT as the standard of care.[9] Around the same time that the NIH consensus statement was issued, preoperative integrated treatments were developed in Europe.[10] The 1997 Swedish Rectal Cancer Trial[11] reported significant improvement in 5-year overall local control and survival with preoperative short-course (SC) RT (5 Gy per 5 fractions, total 25 Gy) followed by surgery, vs surgery alone. Most initial findings on the benefits of adjuvant RTCT in both the preoperative and postoperative settings came from series in which patients received what we now consider inadequate surgery.

The evolution of surgical techniques in European studies culminated in total mesorectal excision (TME), first promoted by Heald, wherein en bloc resection of the rectum with its mesorectum is performed to the levator muscles in the avascular plane outside of the mesorectum. The mesorectum is enveloped by the visceral rectal fascia, which separates it from the parietal endopelvic fascia; sandwiched between the two fasciae lies a thin layer of fat that is filled with loose tissue (the “holy plane of Heald”), containing nerves for the pelvic organs. Embryologically, the rectum and mesorectum (and their vessels and lymphatics) develop together; thus, the plane that describes this resection respects the anatomy and embryological origins.[12,13]

This achievement became the new standard: local failures after TME alone for pT3-4 and N1-2 disease with a medium-risk or low-risk presentation ranged from 15% to 21%,[14] and 5-year local recurrence reached as low as 5%, causing integrated approaches with an adequate and meticulous surgical procedure to be questioned.[15]

European studies concluded that surgical quality significantly influences local recurrence and survival. Quirke proposed three planes, classifying the quality of the respective resected specimens as high, acceptable, or poor: mesorectal plane (intact mesorectum—high quality), intramesorectal plane (minor irregularities of the mesorectal surface—acceptable), and muscularis propria plane (specimen with high loss of mesorectum—poor quality). This classification correlates significantly with survival outcomes.[16]

Studies in the mid-1980s demonstrated that margin involvement was central in effecting local control and that the distance between microscopic tumor penetration and surgical circumferential
resection margin (CRM) was more significant than the distal or proximal margin.[17] European groups have recently reported that magnetic resonance imaging (MRI) predicts the risk of CRM involvement or threat before surgery. MRI can define involvement of the mesorectal fascia (MRF); if the MRF is involved or if the lesion gets as close as 1 mm from the MRF, there is a high risk of a positive CRM if only TME is performed—hence, the proposal of the term “MRF +/−”[18,19]

The “Dutch Trial” (2001) was a multicenter randomized study with certified quality of surgery; it compared TME alone to preoperative SC RT followed by TME. Of the 1861 subjects, local failure rates were better in the integrated treatment arm for stage II and stage III patients than in the surgery-alone arm: 2-year overall local failure was 2.4% and 8.2%, respectively (P < .001) (stage II: 1% vs 5.7%; stage III: 4.3% vs 15%). Survival did not differ (82.0% vs 81.8%).[20] This study supported integrated treatment, even if adequate and certified TME was performed. In the 12-year follow-up update, the 10-year cumulative local recurrence rate was 5% for RT plus surgery and 11% for surgery alone (P < .0001). Overall survival did not differ between the two groups. Notably, in TNM stage III patients who had a negative CRM, 10-year survival was 50% in the RT-plus-surgery group compared with 40% in the surgery-alone group (P = .032).[21] The “Dutch Trial” concluded that a positive CRM was a robust predictor of local recurrence, for which planned postoperative RT, in patients with pathological evidence of CRM positivity, could not compensate.[22]

In 2009, a British group examined whether selective postoperative chemoradiation improved outcomes in the subset of patients with involved or threatened CRMs. The UK Medical Research Council Trial (MRC 07) randomized 1350 cStage I-III patients to preoperative SC RT followed by surgery or to initial surgery followed by postoperative long-course RTCT (with RTCT only for patients with involved or threatened CRMs after surgery). TME was not mandatory but was performed in 92% of cases. At a median of 4 years of follow-up, the preoperative arm had significantly lower local failure rates and better disease-free survival (DFS).[23] In patients with a positive CRM, local recurrence rates did not differ significantly between groups. This trial did not have as an aim comparing SC and LC treatment; rather, it compared the preoperative and selective postoperative approaches.

A German group examined the efficacy of preoperative RTCT (the “German Trial”), randomizing 823 patients with cT3 or cT4 or node-positive disease. One arm received preoperative long-course RTCT (LCRTCT) followed by surgery (with mandatory TME), and the other arm underwent the same surgery, followed by postoperative RTCT; the same RTCT fluorouracil (5-FU)-based regimen (1.8 Gy per fraction, total 50.4 Gy) was administered, except for a boost of 540 cGy in the postoperative arm. The 5-year local failure rate was lower in the preoperative therapy arm (6% vs 13%; P = .006), as were acute and late toxicity rates. Five-year survival did not differ significantly.[24] The 11-year follow-up update confirmed these results.[25]

Based on this and subsequent evidence, the 1990 NIH guidelines are no longer followed in the US, and the postoperative approach is limited to patients with pathological evidence of high risk or who are unable to receive RT preoperatively. Thus, the preoperative RT approach is now preferred, even if adequate surgery is performed; this can be administered in an “SC RT alone” schedule or in LCRTCT (taking advantage of chemosensibilization). It improves local control and (primarily with LC administration) effects pathological complete responses (pCRs) and sphincter preservation, although it has not affected survival in any randomized study in the TME era.

The use of MRI preoperative parameters to tailor treatment can exploit the potential of LCRTCT to manage a positive MRF or a low-lying lesion, as LCRTCT can enhance downstaging more than SC RT. Five meta-analyses have reported conflicting results on survival.[26-30] All demonstrated a decrease in local recurrence rates with preoperative irradiation. Camma et al.[26] and the Collaborative Colorectal Cancer Group[27] reported a survival advantage for the use of preoperative RT. A systematic review of radiation therapy trials by the Swedish Council of Technology Assessment in Health Care (SBU)[28] noted that preoperative RT improved survival by approximately 10%, whereas meta-analyses by Munro and Bentley[29] and Fiorica and Carlei[30] did not. A pooled analysis of post-2000 randomized trial data showed a survival benefit for preoperative RT.[31]

**Which preoperative approach is superior: long-course or short-course?**

Despite a wide consensus regarding preoperative RT followed by TME for locally advanced presentations (eg, T3-T4, N+), the preferred RT remains undetermined (SC RT vs LCRTCT). A recent survey of surgeons from 123 centers in the US, Europe, and Asia with at least 5 years of experience in rectal cancer management noted variations and inconsistencies in the indications for preoperative RT.[32] Of those interviewed, 92% preferred LCRTCT preoperatively. SC therapy was preferred by 10% of US surgeons and 16% of non-US surgeons, although these preferences were insignificant.

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As Minsky has highlighted,[33] the choice of preoperative approach is influenced by historical practices. North American and European groups reported improved results with postoperative RTCT through the 1980s, leading to its shift to the preoperative setting: this preoperative approach was adopted by Central and Southern European countries.

In contrast, since their initial experiences in the 1980s and 1990s, groups such as the Scandinavian, Dutch, and British (who considered systemic CT for colon and rectal cancer as investigational), have been concerned about the risk of additional toxicity from simultaneous RT and CT and have questioned the value of concomitant use of RT and CT. These groups have considered the radiobiological features of various RT schedules and their impact on the biological equivalent dose, and they have preferred to increase the dose per fraction rather than use chemosensibilization to obtain a more effective schedule.[10,34]

The direct comparison of outcomes from phase III trials has failed to indicate the preferred approach: few randomized studies have evaluated this issue by direct comparison. In a Polish trial of 312 patients who received SC RT (and surgery within 7 days) or LCRTCT (with a 5-FU–based chemotherapy regimen) followed by surgery 4 to 6 weeks later, no significant difference in survival and local control was found between groups at a median follow-up of 4 years. However, the LC group had a significantly lower rate of CRM involvement than the SC arm (4% vs 13%).[35] An Australian study[36] randomized 326 patients to similar SC and LC schedules, with postoperative adjuvant chemotherapy in both arms. At a median follow-up of 5.9 years, 5-year survival and 3-year local recurrence did not differ.

Both trials reported significantly higher rates of grade III/IV acute toxicity in the LCRTCT arm.

In a recent review, Buiko lamented the lack of sufficient evidence on local control and survival to suggest the superiority of one schedule or the other.[37] Clinical considerations were not addressed extensively in the Polish and Australian studies. Generally, LCRTCT results in a higher proportion of sphincter-saving procedures and manages threatened or involved CRMs and MRFs better; it can also render an initially unresectable lesion resectable and can effect higher downstaging and pCR rates. Most series have reported improved long-term outcomes and excellent local control rates for patients who achieve a pCR after preoperative RTCT, independent of initial T and N stage.

### TABLE 1

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<th>Main Advantages of Short-Course and Long-Course Preoperative Radiotherapy</th>
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<td>Although increases in pCR rates with RTCT have not improved survival in randomized studies, a recent pooled analysis of randomized trials of preoperative RTCT reported that pCR identifies a subgroup with better survival indicators with regard to local control, distant metastases, and overall survival.[31,38] Few studies have addressed the question of whether surgery can be avoided in the best responders after RTCT.[39,40] In contrast, SC RT (with early surgery) has a low likelihood of inducing a pathological or clinical response because it requires adequate time after radiation-induced biological damage; however, this approach is less demanding, is associated with less acute toxicity (increasing the adherence to protocols), and is shorter in duration than LCRTCT. The chief advantages of SC RT and LCRTCT are listed in Table 1. The payment system should also be considered, since this has influenced the choice of SC RT or LCRTCT in some European countries. For instance, Germany and Switzerland (where LCRTCT is usually preferred, as in the “German Study”) have a fee-for-service reimbursement system that records each service (eg, simulation, planning, treatment session); thus, longer treatments do not pose an economic problem, because they are reimbursed more than shorter treatments. In the Netherlands and the UK (where SC therapy is preferred, as in the “Dutch trial”), reimbursements are made through a budget or case payment. The department receives a set amount of money for each patient or treatment; thus, in some cases, fewer fractions per treatment or less complex therapies are preferred to longer treatments.[41] Two of the most important oncological guidelines are those issued by the National Comprehensive Cancer Network (NCCN)[42] and the National Cancer Institute (NCI) (in its Physician Data Query [PDQ] database).[43] These guidelines are not directly comparable, because the former classifies by T, N, and M parameters, whereas the latter uses stages (0 to IV); the recommendations given by the NCCN for some TNM-based classes of presentations do not always correspond to one single stage-based classification.</td>
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However, both guidelines agree on the treatment approach for locally advanced resectable lesions included in stages II and III; presentations from T3N0 to Tany N+ are grouped together by the NCCN—a system that includes T4N0 (for Stage II per the PDQ schema) and T4N+ (defined as “Tany, N1-2” in the NCCN schema, and corresponding to stage III in the PDQ schema) in the same group of indications. The organization of these guidelines also reflects the fact that even initially unresectable lesions can undergo significant downstaging after integrated treatment (as occurs more often with LCRTCT, although SC therapy is usually preferred for T3 lesions).

Both guidelines recommend a preoperative RTCT 5-FU–based regimen (or oral capecitabine [Xeloda]); transabdominal TME; postoperative RTCT for patients who do not receive preoperative therapy (eg, due to clinical understaging or comorbidities); and eventual adjuvant chemotherapy. The institutions that issued these guidelines are both American; that they recommend that preoperative RT be delivered as LCRTCT is not surprising, given that this schedule is widely used in the US. It is also widely used in Central/Southern European countries, whereas Northern Europe and the UK often use an “SC RT alone” schedule.

The indications in European guidelines vary widely. In 2008, the “EURECA (European Rectal Cancer) project” was conducted in Europe to determine the degree of consensus on several topics, with the aim of improving clinical practice and research. Endorsed by the European Society of Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO), and the European Society of Therapeutic Radiation Oncology (ESTRO), the consensus document was published in 2009.[14] For treatment of intermediate stages (clinically [c] resectable or pathological [p] T3–4 or N1–2 M0), there was moderate consensus that SC therapy reduces local relapse. LCRTCT was also considered one of the primary options; however, LCRTCT was the preferred modality for more advanced unresectable lesions. **TABLE 2**

American and European Guidelines for the Management of Locally Advanced Rectal Cancer

Other guidelines for LARC are summarized in Table 2.[44-50]

Thus, we conclude that due to its potential ability to increase downstaging and pCR and its efficacy in CRMs, LCRTCT is the preferred option for more advanced lesions or cases in which MRI of the MRF shows a risk of involvement. LCRTCT has tremendous potential for lower-lying lesions, increasing the likelihood of organ sparing; it also identifies the best responders and nonresponders to treatment—patients for whom decisions to modulate surgery or intensify postoperative treatments might be made differently, on the basis of the magnitude of their response to LCRTCT (which significantly correlates with prognosis).

**How can difficulties with preoperative approaches be overcome?**

Difficulties with preoperative approaches must be addressed; such difficulties include both the practical aspects of clinical trial evidence and the management of such research, the former of which is being addressed by new, ongoing studies, including the Stockholm III trial, a German study, a Dutch study, and the INTER-ACT study. The Stockholm III trial[51] is randomizing patients to LC RT (without concomitant CT) with delayed surgery, SC RT with immediate surgery, or SC RT with delayed surgery. The last arm was designed to evaluate the potential of SC therapy to produce a pCR. In the interim analysis (the first 303 patients), 12.5% of the patients who received SC RT followed by delayed surgery had a pCR, vs 0.8% of patients who received SC RT with immediate surgery. The German study[52] is comparing SC RT followed by early surgery vs LCRTCT followed by delayed surgery. T2N+ patients will be included, adjuvant chemotherapy will be mandatory for all patients to avoid potential bias, and a large number of patients will be enrolled (760 expected). The Dutch Rectal Cancer and Pre-operative Induction Therapy Followed by Diligent Operation (RAPIDO) trial is comparing LCRTCT followed by surgery and postoperative chemotherapy (with capecitabine and oxaliplatin [Eloxatin]) vs SC RT followed by 6 cycles of the same chemotherapy and surgery.[53] The INTER-ACT study is determining whether intensification of the biological dose with a concomitant RT boost during LCRTCT (and reduction in the overall duration of preoperative RT) increases tumor responses.[54]

Further studies could explore the optimal association of LCRTCT with chemotherapy and new biological agents.
Oral capecitabine is safe and effective compared with a standard 5-FU–based regimen. Both of these drugs have been studied in combination with oxaliplatin, irinotecan, and biological agents (eg, cetuximab [Erbitux], panitumumab [Vectibix], and bevacizumab [Avastin]) in phase I and II studies to determine whether combination therapy improves efficacy. Long-term results are pending from several trials of multidrug preoperative RTCT. Some results are conflicting, and recent evidence throws into question the value of oxaliplatin-based treatment: the European STAR and ACCORD trials reported similar increases in acute toxicity without a corresponding increase in pCR rates. Longer follow-up is needed to determine the impact of oxaliplatin on DFS in these studies. The recent European CAO/ARO/AIO-04 trial showed a significant increase in pCR rates with oxaliplatin and standard treatment. The American National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 and the Pan-European Trials in Adjuvant Colon Cancer (PETACC)-6 studies are investigating this issue.

In a recent comment, Mohiuddin proposed a “switching” strategy that would involve sequential timing along with RT (START): sequential full-dose monochemotherapy cycles would be administered, switching the regimens during therapy, with goals of targeting different cell cycle pathways and potentially different cell populations to overcome resistances. Because the presentations of LARC are not homogeneous, tumor behavior should be examined to tailor treatments and improve outcomes. The inadequate biological and radiological characterization of the adverse features of tumors has necessitated the identification of other means of defining tumor behavior.

With regard to research, two issues have become urgently important: the ability to use large databases (sharing data between institutions) and the availability of surrogate endpoints. Larger databases can increase statistical power and facilitate tests between datasets. Surrogate endpoints can generate results faster, as the endpoint of biochemical failure has done in prostate cancer. For rectal cancers, pCR rate is a valuable surrogate endpoint.

Recent analyses that include data from randomized trials of colon cancer patients who have undergone adjuvant chemotherapy have claimed that 2- and 3-year DFS (2-3yyDFS) is a valid surrogate endpoint for 5-year OS, and even more so for 6-year OS—a correlation that was more robust for stage III colorectal cancer patients. Similarly, a pooled analysis demonstrated that rectal cancer patients who were disease free at 2 years had an OS benefit at 5 and 10 years of follow-up, compared with those who experienced early recurrence.

Use of a nomogram that takes into account the main variables that influenced survival endpoints in a pooled analysis of five European clinical trials has been suggested to help with clinical decision making in rectal cancer.

Longer follow-ups for current studies, the evaluation of good surrogate endpoints in a large database, results from new studies, and the increasing use of tailored treatments for LARC—for example, making wise choices of SC RT vs LCRTCT, avoiding surgery or RT, and using adjuvant postoperative CT for various tumor presentations—will translate into survival gains.

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