Selective use of radiation for locally advanced rectal cancer: one size does not fit all

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ABSTRACT

INTRODUCTION: The last three decades have seen several major advances in the multidisciplinary management of locally advanced rectal cancer (LARC). Although rectal cancer management varies globally, the standard of care for clinical stage II/III rectal cancer in North America remains chemoradiation followed by total mesorectal excision and adjuvant therapy.

EVIDENCE ACQUISITION: In this review we evaluate the evidence for neoadjuvant therapy in LARC and the variety of treatment options available.

EVIDENCE SYNTHESIS: We identify heterogeneity of outcomes in stage II/III rectal cancer, leading to the potential for overtreatment. The PROSPECT trial is a multi-centre, international effort to determine whether a selective approach to provision of radiotherapy in stage II/ III LARC is a viable treatment option. Unlike many other studies, the aim of PROSPECT is to reduce treatment rather than increase the intensity of preoperative therapy.

CONCLUSION: LARC is a heterogeneous disease with varying risk of relapse. Studies are underway to attempt to individualise care to avoid overtreatment while maintaining excellent oncologic outcomes.

Key words: locally advanced rectal cancer, stage II/III rectal cancer, neoadjuvant therapy, radiotherapy, individualised treatment

Introduction

The clinical management of locally advanced rectal cancer (LARC) has become increasingly complex over the past three decades, now requiring multi-disciplinary specialist input from the time of diagnosis to correctly allocate multi-modality treatment. Rectal cancer is distinct from colon cancer, carrying an increased risk of local and regional recurrence resulting from its anatomic location within the narrow confines of the bony pelvis, which makes margin-negative surgical resection difficult. This local recurrence risk has driven major advances in colorectal surgical oncology, including refinements in pre-and post-treatment imaging, improvements in surgical technique and new neoadjuvant therapies. As treatments evolve and knowledge of the disease process builds, rectal cancer management is becoming increasingly personalized, taking into consideration the patient's own informed preferences. The aim of the present review is to provide an overview of modern neoadjuvant therapy for locally advanced rectal cancer and to discuss the rationale behind the selective use of radiotherapy for some patients.

Modern management of LARC with long-course chemoradiation

The current standard for management of LARC in North America includes chemoradiation (chemoRT), total mesorectal excision, and adjuvant systemic chemotherapy [1]. Such a strategy aims to achieve a margin-negative resection whilst managing the dual risk of local and systemic recurrence after surgery. This modern standard is built on the results of the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) R01 study, published over 30 years ago, which demonstrated that pelvic irradiation led to an impressive reduction in local recurrence rates, from 25% to 16% [2]. Since then several landmark trials have gone on to shape modern oncological practice. The German Rectal Cancer Study Group [3] demonstrated the advantage of pre-operative over post-operative pelvic radiotherapy: a marked reduction in both acute and long-term treatment-related toxicity (Grade 3/4 toxicity 27% vs. 40% and 14% vs. 24%, respectively). Subsequently, the EORTC Radiotherapy Group Trial 22921 reported that with the addition of pre-operative fluorouracil-based chemotherapy, local recurrence (LR) rates fell further to below 10% [4]. The FFCD 9203 trial provided further evidence of the benefits of chemoradiation for cT3/4 rectal cancers, demonstrating that in comparison to radiotherapy alone, chemoRT halved the rates of LR at 5 years (8.1% vs. 16.5%) [5]. That trial also found higher rates

of pathologic complete response (pCR) (11.4% vs. 3.6%) with chemoRT, and only a modest increase in treatment-related toxicity (Grade 3/4 toxicity 15% vs. 3%).

Subsequent attempts to refine chemoRT regimens in the intervening years have proven less successful. For example, the addition of oxaliplatin (a drug with proven efficacy in the metastatic and adjuvant settings for colorectal cancer) to neoadjuvant therapy has not yielded impressive results. Six phase III trials (STAR-01, ACCORD-12, NSABP R-04, CAO/ARO/AIO-04, PETACC-A6, and FOWARC) have evaluated oxaliplatin combination chemoRT to date [6-10]; only 2 have reported potential benefit for the addition of oxaliplatin. The German CAO/ARO/AIO-04 trial reported a statistically significant improvement in disease-free survival (75.9% vs. 71.2%) and pCR (17% vs. 13%) with oxaliplatin added to chemoRT; however, its results are potentially confounded by variations in fluorouracil scheduling between treatment arms [8]. The Chinese FOWARC trial reported that FOLFOX-RT was associated with higher pCR rates and increased down-staging compared with 5FU-based chemoRT [10]. Such findings were not reproduced in the four other trials. However, the addition of oxaliplatin was associated with significantly higher rates of Grade 3/4 treatment-related toxicity in 4 of the 6 trials; consequently, 5FU-based chemoRT remains the recommended long-course regimen for LARC according to the NCCN guidelines [11].

No novel radiotherapy combinations for LARC have been demonstrated superior to current neoadjuvant treatments. For example, the addition of targeted therapies including anti-vascular endothelial growth factor (anti-VEGF) and anti-endothelial growth factor receptor (anti-EGFR) agents to long-course chemoRT regimens has been evaluated in phase II trials, but these failed to meet primary endpoints [12-14].

Short-course radiation for cT3/4 LARC

The use of short-course radiation (SCRT) with immediate surgery for cT3/4 LARC is advocated by many oncologists, predominantly from European countries. Short-course radiation involves 25 Gy given over 5 fractions and is considerably less expensive and associated with lower early radiation-related toxicity compared with long-course chemoRT (LCRT) [15]. However, performing surgery early reduces the potential for significant tumour down-staging and also for complete response to treatment.

The Polish and TransTasman trials compared SCRT with LCRT [15, 16]. Though the Polish Colorectal Study Group trial [15] was powered to detect a difference of at least 15% in rates of

sphincter preservation, it failed to meet this endpoint, finding permanent colostomy rates of 56.9% in the SCRT group and 51.6% in the LCRT group in 312 patients. The authors concluded that because survival, distant and local recurrence did not differ between the groups, SCRT was a reasonable alternative to LCRT. However, SCRT was associated with a higher involved circumferential resection margin rate than LCRT (12.9% vs. 4.4%). As expected given that surgery was performed immediately, the pCR rate in the SCRT group was 1% compared with 16% in the LCRT group, demonstrating the down-staging benefits of LCRT.

The Trans-Tasman Radiation Oncology Group trial found no statistically significant differences in overall survival, local or distant recurrence-free survival between SCRT and LCRT (n=163 per group), but did report a trend towards increased LR with SCRT (7.5% vs. 4.4%) [16]. This trend may be confounded by the higher proportion of low rectal cancers in the SCRT group (30% vs. 19%), which have a greater risk of LR compared with mid-upper rectal tumours. Similar to the Polish trial, pCR rates were greater with LCRT (15% vs. 1%), but circumferential margin positivity was comparable (4% vs. 5%). The authors concluded that despite the lack of differences in survival and recurrence, LCRT may be more effective in reducing LR for distal tumours.

SCRT with delayed surgery to some degree overcomes the drawback of SCRT with immediate surgery, as down-staging responses have been demonstrated. After initial non-randomized studies reported more down-staging and pCR in comparison to SCRT with early surgery [17, 18], Stockholm III compared SCRT with immediate surgery, SCRT with delayed surgery, and LCRT in a randomized trial of 840 patients with resectable rectal cancer [19, 20]. In comparison to SCRT with immediate surgery, SCRT with delayed surgery was associated with fewer post-operative complications and higher rates of tumour down-staging, tumour regression and pCR (11.8% vs. 1.7%). The authors concluded that SCRT with delayed surgery was a viable alternative to conventional SCRT. Unfortunately, the trial was limited by a prolonged recruitment period (1998-2013), during which time modifications in rectal management and clinical staging are recognized to have improved outcomes. For example, the LR rate decreased on a population basis from 15% to 5% during the period studied. The introduction of MRI staging in 2003 also influenced patient recruitment by enabling selection of patients with locally advanced tumours in later years.

These trials have not settled the debate regarding which radiation modality should be used routinely in LARC, but they do highlight the importance of considering local staging

characteristics and tumour location when selecting the appropriate therapy. Given the wide spectrum of disease, it may be possible to define groupings of cT3/4 tumours by risk of LR, determining the optimal neoadjuvant strategy. A Northern European strategy developed in the 2000s advised distinct treatments for LARC patients in 'favourable', 'intermediate', or advanced risk categories, also referred to as 'The Good, the Bad and the Ugly' by Blomqvist and Gilmius [21]. Patients with cT3a-b tumours were considered to have low risk of LR and could proceed straight to surgery. The proposed appropriate treatment for those with cT3c or cN+ or low rectal tumours without mesorectal fascial involvement, at intermediate risk, was SCRT followed by surgery, and for patients with cT4 or mesorectal fascial involvement, considered advanced, LCRT or in certain cases SCRT and delayed surgery.

Systemic chemotherapy prior to chemoRT and surgery for LARC

Though neoadjuvant therapy in rectal cancer conventionally consists of pelvic irradiation, interest is growing in the use of systemic chemotherapy prior to surgery. Several trials and single-centre studies have tested the benefit of systemic chemotherapy with 5-FU/ capecitabine and oxaliplatin-based regimens (currently recommended postoperatively) [11, 22-27]. The key benefit of administering adjuvant chemotherapy prior to surgery is the potential to reduce the risk of distant recurrence, which is now substantially more common than LR, by targeting micrometastases at the outset. Preoperative chemotherapy also enables in vivo assessment of chemosensitivity by the degree of tumour regression or down-staging. Finally, tolerance for chemotherapy may be limited in patients recovering from major cancer surgery, sometimes preventing a complete course of treatment. Up to 27% of patients never start adjuvant chemotherapy after rectal resection [28] and 50% don't receive the full dose [29], in many cases as a consequence of prolonged recovery. Giving chemotherapy prior to surgery eliminates the need to defer closure of diverting ileostomies, allowing earlier restoration of gastrointestinal continuity. Preoperative systemic chemotherapy can also induce local tumour regression, which may enable more patients to avoid radiotherapy.

Several institutional series and phase II trials have evaluated the oncological efficacy of induction or consolidation chemotherapy (ICT or CCT) delivered before or after chemoRT in LARC [12, 14, 22, 23, 25, 30]. To date, the literature on this topic is in part limited by a lack of phase III data and adequate control groupings within the studies. Comparisons between North American and European studies are also limited by heterogeneous inclusion criteria, as some

European studies evaluated only high-risk LARC. In general, despite improved compliance and toxicity data, data on response rates are variable; pCR rates range from 14-36% for ICT/ chemoRT based regimens [12, 22, 25]. Despite these limitations, we review the available data in detail in this section.

Several studies suggest that a short 2-cycle course, rather than the standard 4 cycles, of chemotherapy may be sufficient for induction prior to chemoRT. A small phase II study, including 57 LARC patients with cT2-4/ N+ tumours randomized to 2 cycles of ICT with mFOLFOX6 prior to chemoRT or chemoRT alone, found comparable response between the 2 treatment arms, and a 28% pCR in the ICT/chemoRT group [31]. Two institutional series with similar inclusion criteria from Spain and Denmark reported pCR rates of 29% in 52 patients (following 2 cycles of FOLFOX prior to chemoRT) and 23% in 88 patients (after 2 cycles of CapOx prior to chemoRT), respectively [24, 32].

A pooled analysis of data from 269 patients from 2 European phase II trials suggests that chemotherapy followed by chemoRT may be especially beneficial for patients with high-risk LARC, defined as tumour <1 mm from the mesorectal fascia, cT3c/d or T4 tumours, and low tumours involving pelvic floor musculature. The pCR rate was 20.0% among the 240 patients in the EXPERT and EXPERT-C trials who underwent surgery, and T stage and N stage down-staging was observed in 56.6% and 43.4%, respectively [33]. Although both trials lacked a chemoRT-alone control group, these results were thought to represent improvements in treatment response with good long-term disease control in a high-risk population. Furthermore, compliance with treatment was good and toxicity was minimal [14, 22].

The Spanish GCR-3 phase II randomized trial found that the key benefit of ICT is improved delivery of treatment, due to better toxicity profiles [30]. GCR-3 compared short- and long-term outcomes between 49 high-risk LARC patients treated with chemoRT and then surgery (71% of whom received postoperative adjuvant chemotherapy_ with those of 54 patients treated with ICT (CAPOX) followed by chemoRT. Grade 3/4 toxicity was reported in 19% of patients in the ICT arm compared with 54% in the postoperative chemotherapy arm. The study found no difference in pCR rates (13 vs. 14%) or 5-year local (2 vs. 5%) or distant (21 vs. 23%) recurrence rates between the groups. The trial defined high risk LARC as tumours within 12 cm of the anal verge with the following features: extending to within 2 mm of the mesorectal fascia, cT3 tumours in the lower third of the rectum, cT4 disease, and/or cN+ disease. The fact that the ICT group

contained a higher number of T4 tumours (13% vs. 6%) and low T3 tumours (32% vs. 23%) than the chemoRT group may have limited power in detecting differences in response.

The AVACROSS study [12] found a much higher pCR rate (36%) for ICT with XELOX and bevacizumab, evaluated in 45 patients with high-risk LARC, defined similarly to the GCR-3 study. However, 2 of the 47 enrolled patients died during neoadjuvant treatment, and there were higher-than-average rates of surgery-related complications (including anastomotic leaks in 5 of 47 patients and need for re-operation in 11 of 47 (24%)) after treatment with the bevacizumab-based regimen.

Memorial Sloan Kettering reported that in a small cohort of patients with LARC treated with ICT followed by chemoRT, the addition of FOLOX was associated with a substantial increase in tumour down-staging and a 36% pCR rate [26]. A recent follow-up study found that ICT was associated with higher received doses of 5-FU and oxaliplatin and more patients completing the planned regimen compared with standard preoperative chemoRT with planned postoperative adjuvant chemotherapy [27]. Specifically, 78% of the 308 patients receiving ICT completed 8 cycles including oxaliplatin chemotherapy compared to 41% of the 320 who had post-operative therapy. The complete response rate with the addition of ICT was 36% compared with 21% treated with preoperative chemoRT alone.

The timing trial published by Garcia-Aguilar and colleagues in 2016 demonstrated good tolerance of systemic chemotherapy delivered after chemoRT and prior to surgery [34]. More cycles of FOLFOX were associated with greater rates of tumour regression and pCR. It is not possible to determine to what extent the increased time delay to surgery from completion of radiation contributed to these impressive responses (up to 38% with 6 cycles of FOLFOX), but these results add to the evidence that preoperative chemotherapy may lead to significant tumour down-staging.

Heterogeneity in outcomes and LR within LARC—one size does not fit all

We have now reached an era in which trials of neoadjuvant regimens consistently report very low LR rates, now in single digit percentages. Consequently, LR risk will rarely be a primary endpoint in future trials due to the large number of patients required to detect significant differences in LR rates. Rectal cancer management has also advanced in many other ways, most notably through the widespread adoption of total mesorectal excision (TME) and increasing specialisation in colorectal surgery over the past 30 years. TME consists of precise anatomical

excision of the rectum within its enveloping mesorectum by dissecting sharply between the visceral and parietal layers of the endopelvic fascia. This procedure ensures complete removal of all draining loco-regional lymph nodes, achieving higher rates of clear circumferential resection margins, minimising blood loss and injury to autonomic pelvic nerves. TME has not been formally tested in randomised clinical trials, but is widely considered to have been a major contributor to improved local recurrence rates [35-37]. The widespread adoption of the technique has also driven improvements in surgical training and rectal cancer surgical specialisation [38], further contributing to improved oncological outcomes.

Evidence is increasing that TME alone is sufficient to treat tumours considered to have good prognosis based on MRI staging. Low LR rates (1.7%) were reported by the Mercury study group in a prospective non-randomised observational study in which 122 patients with cT3a-b tumours (regardless of clinical N stage) were treated by TME without neoadjuvant therapy [39]. However, the distant recurrence rate in this cohort was 19%.

Another study supporting individualised treatment was the Dutch rectal cancer trial, published in 2001 [40]. One of the first studies examining the influence of preoperative pelvic radiation on LR in the era of improved surgical quality via total mesorectal excision, the trial demonstrated that SCRT was associated with significantly fewer recurrences than surgery alone. The long-term results also showed that SCRT appeared to be more beneficial for patients with lower-lying tumours, tumours with clinical nodal involvement, or tumours not encroaching on the surgical circumferential resection margin [41]. Of note, despite a well-defined operative technique, patients who had poorer quality resection specimens had worse long-term survival [42]. Other results confirm the critical importance of surgical technique is in rectal cancer management [43].

Criticism is mounting of the definition of LARC as clinical stage II and III, as this group of tumours is heterogeneous and current staging fails to adequately account for local spread. Several studies indicate that LR risk can be stratified based on T and N staging. In 2002, Gunderson and colleagues analysed the outcomes of 2551 patients from 3 North American rectal cancer trials to generate the following categories of LR risk: low, T1/2N0; intermediate, T1/2N1 and T3N0; moderately high, T1/2N2, T3N1, andT4N0; and high, T3N2 and T4N1/2 [44]. LR rates were lower in the intermediate risk group (6-8%) compared with the moderately high (8-15%) and high-risk (15-22%) groups. Similarly, the highest T and N stages were associated with greater risk of distant metastases (T3N2 45% and T4N2 50%). These data further indicate that

pelvic irradiation may not be required for patients with T1/2N1 or T3N0 stage cancer as long as high quality TME with clear margins is performed.

Later studies supported these correlations between T/N staging and LR risk and revealed their relationship to individualisation of treatment. In 2002, the Intergroup 0114 trial of adjuvant therapy in rectal cancer reported LR rates of 9% among patients with T1/2N+ or T3N0 tumours and 18% among those with T3N+ or T4 [45]. An analysis by Gundersson and colleagues in 2004 [46] of 5 phase III North American trials including 3791 patients reported that in patients with T1/2N1 or T3N0 rectal cancer, the addition of radiation to combined modality treatment did not appear to improve long term disease-specific or overall survival. Together, these results demonstrate that the heterogeneity of outcomes in stage II and stage III rectal cancer calls for individualisation of treatment. For patients with locally advanced rectal cancer, one size does not fit all.

Disadvantages of pelvic radiotherapy and potential for overtreatment

Pelvic irradiation remains the current standard for cT3/4/ N+ locally advanced rectal cancer in many countries, but in patients considered to have low risk of loco-regional relapse, the risk of overtreatment must be considered given the toxicity of radiotherapy. Short-term toxicities are common, and often affect the patient's ability to complete treatment. These include pelvic fibrosis, which can make surgical resection more challenging, and autonomic nerve injury, which can cause sexual, bladder and bowel dysfunction. Quality of life is reported to be lower in patients treated with radiotherapy compared with those who do not [41]; up to 50% of patients who have chemoRT followed by TME report incontinence of stool, faecal urgency and having to wear a pad [47, 48]. Other risks of radiation to the pelvis include small bowel injury with associated long-term enteritis, and depletion of pelvic bone marrow, which can limit tolerance for cytotoxic chemotherapy. As rates of LR after combined modality treatment and TME for rectal cancer are now very low, the challenge ahead lies in addressing the balance of oncologic success with the risk of long-term sequelae and impaired quality of life.

The Preoperative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy Trial (PROSPECT)

The PROSPECT trial (NCCTG-N1048; PROSPECT stands for Preoperative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy and TME) is a large,

multicentre phase II/III trial which compares whether standard chemoRT can be replaced in selected patients with neoadjuvant FOLFOX (Figure 1). The rationale for the trial is the recent results (discussed above) indicating that not all patients require RT, particularly if LR risk is low. In addition, systemic chemotherapy prior to surgery is well tolerated and appears to induce down-staging responses whilst potentially mitigating systemic relapse risk.

In PROSPECT, patients with intermediate-risk LARC (T1/2N1, T3N0, T3N1) without involvement of the circumferential resection margin and who are candidates for sphincter-preserving surgery are randomly assigned to 2 groups: 'standard' or 'selective' management. In the standard arm, patients receive preoperative chemoRT (5FU- or capecitabine-based LCRT followed by TME and then adjuvant FOLFOX chemotherapy for 8 cycles). In the selective arm, patients receive 6 cycles of FOLFOX prior to being restaged; those with $\geq$ 20% clinical response proceed to surgical resection followed by 6 cycles of adjuvant FOLFOX, while those with < 20% response are recommended to be treated with conventional chemoRT followed by surgery and 2 cycles of adjuvant FOLFOX. In the selective arm, patients who do not receive pre-operative chemoRT and have a disease-positive circumferential surgical resection margin are also given post-operative chemoRT. The trial will determine whether the selective approach is a reasonable alternative to conventional chemoRT; that is, whether it leads to similar short-term surgical and long-term oncological outcomes (local and distant recurrence).

The phase II single-centre pilot study recruited 32 patients who were candidates for sphincter-preserving surgery [49]. On clinical staging 23 (72%) had stage III (cN+) tumours, 29 (91%) were cT3, and 3 tumours were cT2N+. Of the 30 patients who completed 6 cycles of FOLFOX-based preoperative chemotherapy, all 30 demonstrated tumour regression and 8 had complete responses. All patients underwent R0 resections and no local recurrences were detected at a median of 54 months follow-up; 4 patients developed distant metastatic recurrence. Only 2 patients did not complete the treatment plan due to chemotherapy-related cardiac toxicity. These results suggest that omission of radiotherapy may be acceptable in a subset of patients with LARC, providing preliminary data supporting the full phase II PROSPECT trial. At the present time, the trial has moved from phase II to phase III and is near its target accrual of 1140 patients.

Summary

In summary, the past 3 decades have seen an evolution in the management of locally advanced rectal cancer. Preoperative imaging has been optimised, surgical techniques have improved, and

multimodality therapy has been applied widely, and as a consequence local recurrence is no longer common. As we progress in the 21st century, mitigation of systemic relapse risk is now the principal challenge, whilst limiting toxicity from potential overtreatment. Individualisation of therapies will become increasingly commonplace, based on baseline imaging assessments and patient choice. The PROSPECT trial, which is close to completion, will determine whether RT may be selectively administered in stage II/ III LARC based on response to induction chemotherapy, which would limit treatment-related toxicity by avoiding overtreatment.

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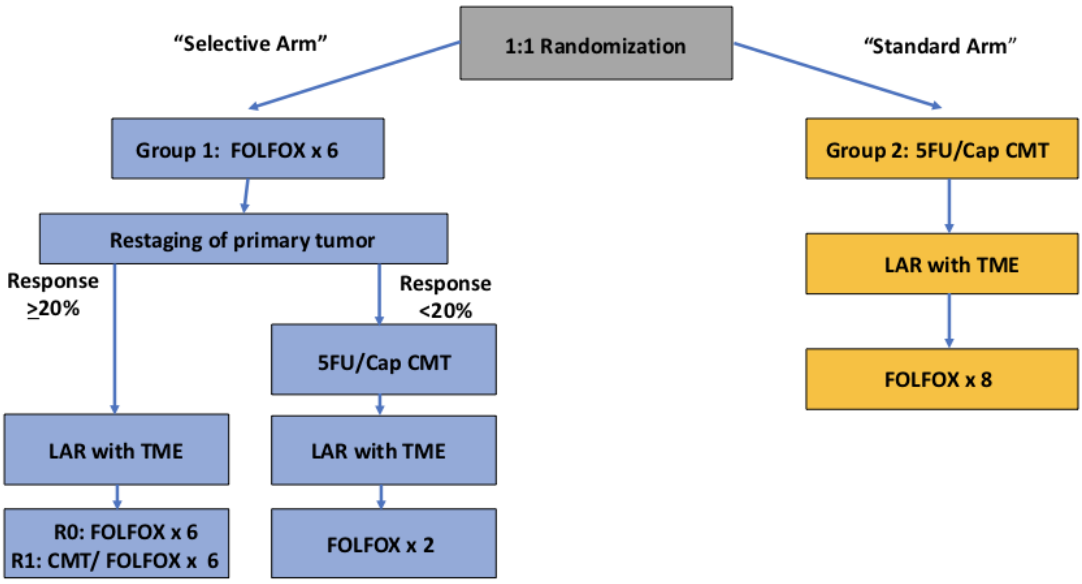

Figure 1. Design of the PROSPECT randomized multi-centre phase II/III trial (NCCTG-N1048). Pre-operative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy and TME compares neoadjuvant FOLFOX with selective use of chemoRT in LARC. CMT, 5-FU/capecitabine + RT; Cap, capecitabine; LAR, low anterior resection; TME, total mesorectal excision.