REVIEW ARTICLE

Neoadjuvant therapy and subsequent treatment in rectal cancer: balance between oncological and functional outcomes

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Abstract:

Current practice of neoadjuvant therapy and total mesorectal excision (TME) in rectal cancer bears the weakness in systemic disease control and long-term functional outcomes. With increasing concerns of the balance between cure and quality of life, new strategies are developed to better oncological outcomes at least cost of function damage. Attractive options to adjust neoadjuvant modality include escalation of radiotherapy, intensification of chemotherapy, and chemoradiotherapy with consolidation or full-course chemotherapy. Subsequently, organ-preserving strategies have gained the popularity. Surgical or nonsurgical approaches that spare the rectum are used as possible alternatives for radical surgery, though high-quality TME remains the last resort to offer reliable local disease control. This review discusses new strategies of neoadjuvant therapy and subsequent management, with a specific focus on the balance between oncological and functional outcomes.

Keywords:

neoadjuvant therapy, rectal cancer, functional outcomes, organ preservation

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Introduction

The development and adoption of multimodal treatment have complicated the management of rectal cancer, with increasing concerns of the balance between cure and quality of life (QoL). Neoadjuvant (chemo) radiotherapy followed by total mesorectal excision (TME) is widely recommended for patients with locally advanced cancer, which is based on the evidence of optimized local disease control[1-3]. However, the approximately 30% risk of distant metastasis after this multimodal treatment remains the leading cause of disease-related death for rectal cancer patients[3-5]. Interest into new strategies of neoadjuvant therapy and subsequent treatment are increasing rapidly, because of not only the unfavorable distal recurrence but also the associated morbidity and dysfunction[6,7].

Although preoperative radiotherapy (RT) is the main pillar of neoadjuvant treatment, multiple studies have focused on modality adjustments, including RT escalation, chemotherapy intensification, and chemoradiotherapy (CRT) with consolidation or full-course chemotherapy, with intent to achieve better oncological outcomes[8]. In addition to investigations in neoadjuvant modality, there has been much progress in subsequent management tailored to the tumor response. Neoadjuvant therapy may result in extensive tumor regression and even complete pathological response (pCR). For patients with complete response identified before surgery, the emergence of organ-preserving strategy avoids definite surgery and associated morbidity, leading to satisfactory oncological results and excellent functional outcomes[9]. Radical surgery with TME technique, however, remains the last resort for patients with incomplete tumor re-
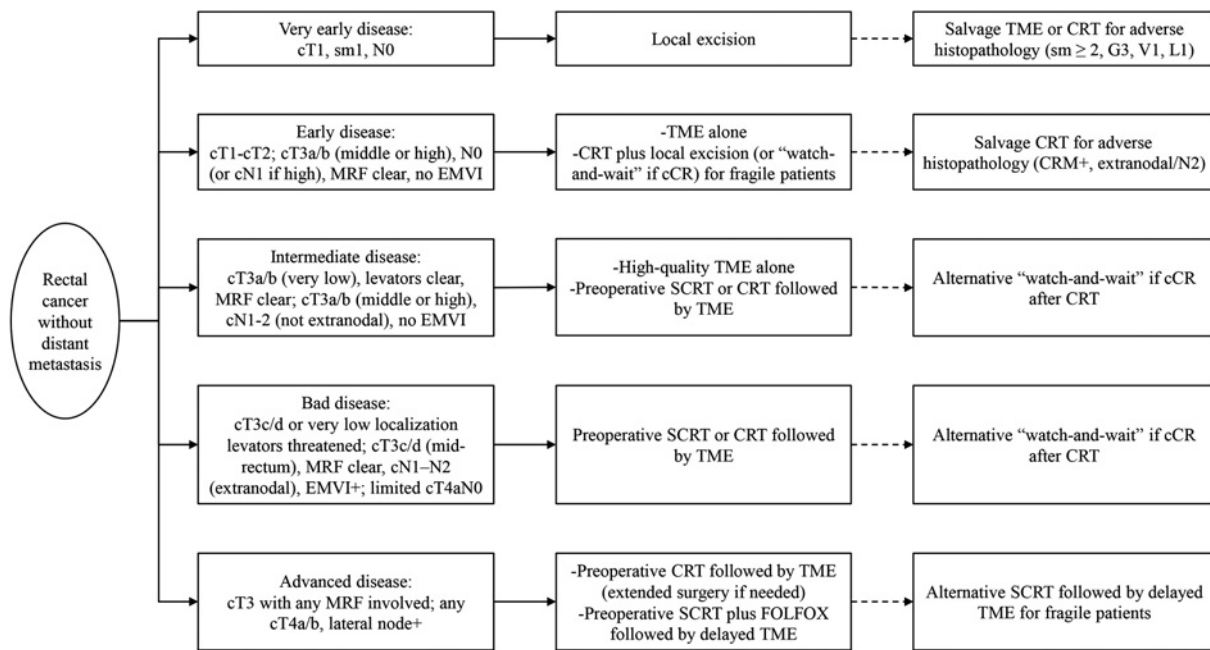
Figure 1. Risk-adapted treatment of rectal cancer without distant metastasis according to ESMO guidelines. cCR, clinical complete response; CRT, chemoradiotherapy; EMVI, extramural vascular invasion; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNM, tumor, node, metastasis.

sponse to achieve favorable local disease control. Modified approaches concerning reconstructions and radiation damage within the pelvis may relieve the adverse effect on functional outcomes[10]. This review discusses these strategies of neoadjuvant therapy and subsequent management in rectal cancer.

Standard Therapy and Indications

Neoadjuvant (chemo) radiotherapy followed by TME has revolutionized the oncological outcomes of patients with resectable rectal cancer in last decades, leading to a local recurrence rate as low as 5%-6%[2,11]. Neoadjuvant treatment also contributes to the tumor downstaging and downsizing, which facilitate surgical resection and sphincter preservation. As a result, current guidelines support the role of multimodal treatment for patients with locally advanced disease[12]. The indications for neoadjuvant (chemo) radiotherapy have been recently further detailed with adaption of recurrence risk[13]. Although TME of high quality is generally recommended, neoadjuvant treatment is specially advised for patients with intermediate to advanced disease to achieve a better local disease control (Figure 1).

Preoperative RT, as the mainstay of neoadjuvant therapy for rectal cancer, includes two typical modalities. The long-course treatment involves conventional fractionated RT (total dose of 45-50 Gy in 25-28 daily fractions), concurrent fluorouracil (FU)-based chemotherapy, and surgery per-

formed within 6-8 weeks. The short-course treatment includes hyperfractionated radiation (total dose of 25 Gy in five daily fractions) followed by immediate surgery within 10 days from the first fraction. Comparisons between long-course CRT and short-course radiotherapy (SCRT) showed no significant differences in oncological outcomes or general toxicity[4,14,15]. However, the systemic disease control is unfavorable after either multimodal management, with an overall rate of distant metastasis in excess of 25%[3,5]. Therefore, new strategies are needed to improve long-term prognosis.

Strategies to Improve Oncological Outcomes

Neoadjuvant therapy may lead to extensive tumor regression with decreased primary tumor size (downsizing), potential nodal sterilization (downstaging), and even no residual tumor found in the resected specimen (pCR). In a subset of patients undergoing neoadjuvant therapy, complete regression of primary tumor could be detected before radical surgery by thorough assessment, without any clinical, endoscopic, or radiologic evidence of residual tumor, and referred to as the clinical complete response (cCR)[16].

Neoadjuvant treatment in rectal cancer is reported to result in pCR in 15%-42% of cases[17,18]. The association between pCR and improved long-term outcomes has been increasingly reported[19]. In a pooled analysis incorporating 3105 patients, those with pCR showed significantly higher rates of 5 year disease-free survival (DFS, 83% vs 66%, $p <$

0.0001) and distant-metastasis-free survival (89% vs 75%, p < 0.0001), and lower rate of 5-year local recurrence (3% vs 10%, p < 0.0001), compared with patients who did not enjoy pCR[17]. A retrospective study divided 725 patients treated with CRT for locally advanced cancer into three categories by tumor response: ypT0N0 (i.e., pathological T0N0 after neoadjuvant therapy) as complete response, ypT1-2N0 as intermediate response, and ypT3-4 or N+ as poor response[20]. The results showed significantly improved 5 year recurrence-free survival (91% vs 79% vs 59%; p < 0.001), 5 year local recurrence (0% vs 1% vs 4%; p = 0.002), and 5 year distant metastasis (7% vs 10% vs 27%; p < 0.001) in patients with complete tumor response. The update of CAO/ARO/AIO-94 trial reported 10 year cumulative incidence of DFS and distant metastasis in 386 patients with different tumor regression after neoadjuvant CRT[21]. Complete tumor regression was confirmed to be associated with the improvement in long-term DFS (90% vs 74% vs 63%, p = 0.008) and distant metastasis (11% vs 29% vs 40%, p = 0.005). These efforts have established the tumor response to neoadjuvant therapy as an early surrogate of long-term oncological outcomes, where pCR should be aimed at by the treatment initiative.

Escalation of radiotherapy dose

Radiotherapy dose escalation is a direct approach to increase the tumor response. Some retrospective studies have shown that a total dose of >50 Gy provides better local control than the lower doses[22]. Nonetheless, the normal tissue tolerance limits the dose escalation, thus various RT techniques are explored to enhance the local boosts. The lyon R 96-02 trial compared the RT regimen of 39 Gy in 13 fractions with endocavitary boost (85 Gy in three fractions) followed by the 13 × 3 Gy[23]. The cCR rate increased in dose escalating group (2% vs 24%, p < 0.05). Another randomized trial compared neoadjuvant CRT of 50.4 Gy with combined CRT and high-dose rate brachytherapy (5 × 2 Gy) in 248 patients with locally advanced cancer[24]. The proportion of major response was higher in the brachytherapy group (29% vs 44%, p = 0.04), but the pCR rate was 18% in both groups. This result indicates a major defect in localized dose escalation, which is the disability to cover lymph nodes with high risk. A promising alternative is intensity modulated radiotherapy (IMRT) that provides an integrated and simultaneous radiation boost to the suspicious lymph nodes, but reliable data of pCR is still warranted[25].

Intensification of chemotherapy

The strategy to intensify neoadjuvant CRT with additional oxaliplatin to FU-based chemotherapy has been investigated by several randomized trials in an attempt to improve local control and long-term survival. So far, the results have been conflicting with variations in the dosing and duration of chemotherapy used. Most studies reported increased toxic effects without significant improvement in pCR achievement[26,27], except for CAO/ARO/AIO-04 study presenting higher rates of pCR (17% vs 13%, p = 0.031) and 3 year DFS (76% vs 71%, p = 0.03) after FU-based CRT with oxaliplatin[28]. In a recent FOWARC trial, 495 patients with clinical stage II/III cancer were randomized to three treatment groups: long-course RT with full-dose 5-FU followed by surgery, the same regimen plus intravenous oxaliplatin (RT+mFOLFOX6), or mFOLFOX6 alone followed by surgery[29]. The preliminary results showed that administering full-dose mFOLFOX6 coupled with RT provided a significantly higher rate of pCR (28%), compared with FU-RT (14%) or mFOLFOX6 alone (7%).

Delayed surgery

Increasing the interval between neoadjuvant therapy and surgery has been widely used to enhance tumor downstaging and downsizing. Several retrospective studies also demonstrated that prolonged intervals after CRT improve the tumor response and ultimate pCR rate[30-32]. Most data suggest that a delayed surgery of >6-8 weeks from the end of CRT contributes to more patients without residual tumor. Results from a large population-based study showed that the optimal time interval to achieve tumor response is 10-11 weeks from CRT completion[33]. There is also evidence of a delayed surgery after SCRT leading to better response. The Stockholm III trial included 840 patients who were randomly assigned to 5 × 5 Gy RT with immediate surgery (within 1 week) or delayed surgery (4-8 weeks), or 25 × 2 Gy RT with surgery after 4-8 weeks[15]. The ultimate analysis showed that the proportion of ypStage I increased from 27% of patients with SCRT plus immediate surgery to 39% of patients with SCRT plus delayed surgery, which was also higher than 29% of patients with long-course RT and delayed surgery. However, no significant differences were found in local recurrence, distant metastasis, or overall survival (OS) between the three treatment groups.

Consolidation chemotherapy

The prolonged waiting period between neoadjuvant therapy and surgery is accompanied by a risk of disease progression. The treatment strategy by adding chemotherapy during the interval may prevent the possible distant metastasis as well as enhance the downstaging of primary tumor. A multicenter non-randomized trial, consisting of four sequential treatment groups of 259 patients with stage II/III disease, evaluated the improvement of pCR after neoadjuvant CRT with progressively longer intervals and additional mFOLFOX6 before surgery[34,35]. This phase-2 study by Garcia-Aguilar et al showed that the extended intervals with consolidation chemotherapy were associated with significantly higher rates of pCR (25% for 12 week interval with

two cycles of mFOLFOX6, 30% for 16 week interval with four cycles of mFOLFOX6, and 38% for 20 week interval with six cycles of mFOLFOX6, respectively), when standard CRT with an interval of 6-8 weeks offered pCR in 18% of the patients ($p = 0.004$). These data were paralleled by the improvement in cCR rate achieved in studies by Habr-Gama et al. The investigators initially reported a cCR rate of 27% for patients undergoing standard CRT (50.4 Gy with two cycles of concurrent 5-FU/leucovorin)[36]. This proportion was markedly increased by extended CRT with consolidation chemotherapy (54 Gy with three cycles of 5-FU/leucovorin during RT and three cycles in the waiting period). Of 70 eligible patients, 39 (57%) patients achieved sustained cCR and 35 (50%) never required surgery after a median follow-up of 56 months[37,38]. Recently, this group performed a direct comparison between standard CRT and extended CRT with consolidation chemotherapy and assessed tumor metabolic activity by sequential imaging with positron emission tomography[39]. After a 12 week interval from RT completion, patients were found more likely to develop pCR or cCR undergoing consolidation CRT (23% vs 66%, $p = 0.004$). Moreover, the additional chemotherapy substantially decreased the probability of tumor regaining metabolic activity in the waiting period (51% vs 18%, $p = 0.004$). These findings support the contribution of additional chemotherapy to the improvement in tumor response rather than prolonged intervals alone.

The consolidation treatment by adding chemotherapy after SCRT is another attractive schedule, as full-dose neoadjuvant chemotherapy could be performed in a relatively short overall time to surgery. A single-arm prospective study involved 76 patients with advanced cancer (T3-4, any N, any M) who underwent 5 × 5 Gy RT followed by four cycles of FOLFOX and surgery 4-9 weeks after chemotherapy completion[40]. Favorable tumor response was observed in 21 (28%) patients of ypT0 and 19 (25%) patients of ypT0N0. In a Polish phase-3 trial enrolling 515 eligible patients with fixed T3-4 disease, either 5 × 5 Gy RT followed by three cycles of FOLFOX or long-course CRT with concurrent FOLFOX was delivered[41]. Although similar rates of R0 resection (77% vs 71%), pCR (16% vs 12%), 3 year DFS (53% vs 52%), local recurrence (22% vs 21%), and distant metastasis (30% vs 27%) were shown between the treatment groups after a median follow-up of 35 months, better 3 year OS (73% vs 65%, $p = 0.046$) and less acute toxicity (75% vs 83%, $p = 0.006$) were presented in favor of SCRT with consolidation chemotherapy. More concrete evidence of this strategy is waited for the ongoing RAPIDO study, which compares 5 × 5 Gy RT followed by six cycles of capecitabine plus oxaliplatin (CAPOX) with standard CRT with capecitabine[42].

Induction/full-course chemotherapy

The failure in systemic control after multimodal treatment is usually attributed to the localized effect of RT and insufficient dosing of concurrent chemotherapy[43]. Moreover, the lack of compliance in postoperative chemotherapy further attenuates the efficacy of systemic treatment[44]. Presence of morbidity after surgery is found as the most frequent reason why patients refuse adjuvant chemotherapy, leading to <50% of patients with full-dose chemotherapy and 27% without any adjuvant treatment[45]. As a result, strategies of induction chemotherapy and full-course chemotherapy before surgery have been introduced to overcome the shortage of current modality.

A single-arm phase-2 trial investigated the approach of induction chemotherapy in 105 patients with locally advanced cancer of poor prognosis defined by magnetic resonance imaging (MRI)[46]. Study treatment consisted of four cycles of CAPOX (12 weeks) followed by 6 week CRT with capecitabine, and surgery 6 weeks thereafter followed by 12 week adjuvant chemotherapy of capecitabine. At surgery, pCR was found in 20% of patients; 3 year progression-free and OS were 68% and 83%, respectively. A similar schedule was evaluated in 84 patients with T3-4 tumor at high risk of disease recurrence[47]. Patients received two cycles of CAPOX followed by CRT with capecitabine and surgery 6 weeks afterwards. At surgery, T downstaging and pCR were observed in 69% and 23% of patients, respectively; 5 year DFS and OS were 63% and 67%, respectively.

More recently, multiple studies have investigated a new option to deliver full-course systemic chemotherapy in the neoadjuvant setting (total neoadjuvant therapy, TNT). In a retrospective study including 61 patients with stage II/III cancer, 28 patients received eight cycles of FOLFOX as the initial treatment before CRT; the others received the same CRT and split FOLFOX before and after surgery[48]. Overall, 22 (36%) patients achieved either pCR (21%) or cCR (15%). Among the 28 patients who received full-course FOLFOX before surgery, 8 achieved pCR (29%) and 3 with cCR (11%). However, these encouraging data were not replicated in the Spanish Grupo Cancer de Recto 3 (GCR-3) trial[49]. In the GCR-3 trial, 108 patients with locally advanced cancer were randomized to receive CRT with concurrent CAPOX followed by surgery and four cycles of adjuvant CAPOX, or four cycles of induction CAPOX followed by the same CRT and surgery. Better treatment completion (54% vs 91%, $p < 0.0001$) and less grade 3/4 chemo-related toxicity (54% vs 19%, $p = 0.0004$) were observed in the TNT arm with induction chemotherapy, but tumor downstaging (58% vs 43%) or pCR rate (13% vs 14%) was not increased significantly. One possible explanation for the similar pCR rates between treatment arms is the parallel interval from CRT to surgery, which plays a vital role in

driving tumor regression. The update of GCR-3 trial has validated the prognostic effect of tumor response to neoadjuvant therapy, showing similar long-term outcomes between the treatment approaches (5 year DFS, 64% vs 62%; 5 year OS, 78% vs 75%)[50]. Further investigation to TNT has been initiated in patients undergoing CRT plus induction or consolidation chemotherapy. In a phase-2 trial aiming at 3 year DFS, patients will be randomized to receive eight cycles of FOLFOX or equivalent CAPOX followed by standard CRT, or CRT followed by chemotherapy of the same regimen[51]. Subsequently, patients who achieve cCR will proceed to a nonsurgical management with close surveillance, and those with residual tumor will undergo TME. This study is designed to examine the efficacy of TNT strategy with two major chemo-schedules, as well as to maximize the proportion of patients who are eligible for organ preservation.

Toxic Effects and Dysfunction

The adoption of neoadjuvant (chemo) radiotherapy and TME brings definite benefits in oncological outcomes at cost of substantial toxicity and dysfunction after surgery. Acute major toxicity from CRT may occur in 10%-28% of the patients, and the incidence of treatment-related complications could reach up to 54%[29,52,53]. The adverse effect is important, especially for patients who respond poorly to the multimodal treatment but endure the downsides of strategy. The awareness of QoL in long-term cancer survivors calls for increasing concerns on the balance between cure and side effects.

Preoperative radiation is confirmed to impair the wound healing, with perineal wound complications found in approximately 35% of patients undergoing abdominoperineal resection after (chemo) radiotherapy[5,52]. The issue of anastomotic complications including the most feared leakage and late stenosis, however, has not been addressed with agreement. Large population-based studies have identified neoadjuvant (chemo) radiotherapy as the independent risk factor of anastomotic leakage[54,55]. But results of randomized trials showed no correlation between SCRT and anastomotic leakage[56], and no significant difference in rate of anastomotic leakage by comparing preoperative and postoperative CRT[2,5]. Contrary to these indirect evidence, the FOWARC trial showed significantly higher rates of anastomotic leakage in groups of FU-RT (19.8%) and mFOLFOX6-RT (18.1%), compared with the group of mFOLFOX6 alone (7.9%)[29]. Moreover, anastomotic leakage was presented as the primary factor to the development of stenosis, and radiation damage played a role in the compromise of anastomosis[57]. Further investigation evaluating the histopathological features of resection margins found certain changes after RT, suggesting the possibility of unhealthy anastomoses using injured bowel at both ends after pelvic radiation[58].

The influence of multimodal treatment on functional outcomes is another major factor that should be taken into account in the decision making. Preoperative RT combined with TME has been well reported to cause severe bowel dysfunction after low anterior resection (LAR), most typically consisting of a constellation of symptoms that include fecal urgency, incontinence, clustering of stools, and frequent bowel movements[59,60]. This so-called low anterior resection syndrome has been shown to occur in 20%-70% of the patients, and seriously impact on QoL from the beginning to even more than a decade after primary surgery[61-63]. A recent cross-sectional study demonstrated the striking prevalence of bowel dysfunction after CRT and radical surgery, showing 84% of the patients affected and 58% with major LARS[64].

Similar problems are reported in the sexual and urinary function after (chemo) radiotherapy and TME, especially for male patients. An observational study prospectively recorded patient-reported outcomes in 149 patients who received neoadjuvant CRT, showing that male sexual function was highly impaired throughout the study period with maximal changes at 12 months after treatment[65]. The same conclusion was drawn by a recent hoc analysis of FOWARC trial, which presented significant erectile and urinary dysfunctions in male patients undergoing CRT at 12 months after surgery[66]. Long-term results come from a follow-up of 4-12 years to 105 patients of a randomized phase-3 study by Braendengen et al[67]. Among the 78 responders, about 25% suffered from urinary incontinence, and most male patients reported severe erectile dysfunction.

New strategies in neoadjuvant therapy bring additional uncertainty to side effects. Adding oxaliplatin to FU-based CRT has been proven to increase acute toxicity, particularly the hematologic and GI toxic effects[26,27,29]. Nonetheless, there is no evidence that the addition of oxaliplatin is associated with increased surgical morbidity or dysfunction. The prolonged interval from RT by delayed surgery and consolidation chemotherapy is likely to cause excessive fibrosis in previously irradiated fields. The question of whether this pelvic fibrosis is associated with surgical morbidity has not been well answered. The aforementioned study by Garcia-Aguilar et al evaluating patients with different intervals from CRT to surgery found progressively increased grade3/4 toxicity along with consolidation chemotherapy (4%-35%) and worse tissue fibrosis after prolonged waiting periods, but no detrimental effect on technical difficulty or postoperative morbidity[34,35]. By contrary, in the GRECCAR-6 trial comparing CRT regimens with 7 or 11 week interval, increased morbidity and worse quality of TME were observed in the 11 week group, owing to the time-related fibrotic changes in surgical fields[68].

Strategies to Improve Functional Outcomes

Treatment decision making is challenging for patients in need of neoadjuvant therapy, considering the tradeoffs between benefit in oncological prognosis and damage in functional outcomes. Despite expert guidelines on use of neoadjuvant (chemo) radiotherapy, common people seem to highly value functional outcomes in preference to surgery alone with tolerance of impaired survival[69,70]. Therefore, individualized treatment is necessary with adequate information of cure and toxic effects. Increasing awareness of QoL beyond survival has shifted the focus onto new strategies to improve functional outcomes without oncological compromise.

Neoadjuvant chemotherapy without radiotherapy

The evil side of RT has raised the question whether neoadjuvant chemotherapy without radiation is an effective and safe option for selected patients, so that associated morbidity and dysfunction could be largely avoided. The GEMCAD 0801 trial investigated a strategy to omit RT and add bevacizumab to three of four cycles of neoadjuvant CAPOX in 46 patients with T3 tumors located in the middle-third rectum without mesorectal involvement[71]. The results showed overall response rate of 78% and pCR rate of 20%; 2 year local recurrence and DFS were 2% and 75%, respectively. However, the unexpected toxicity limits further use of this regimen. A similar strategy was studied by a pilot trial of 32 patients, who received six cycles of neoadjuvant mFOLFOX6 with bevacizumab in the first four cycles[72]. Salvage CRT was provided to two patients intolerant of bevacizumab. All patients had R0 resection, and 25% achieved ypT0-1; 4 year DFS was 84%, and no local recurrence was detected. The ongoing PROSPECT trial based on these preliminary data is recruiting patients with tumor of cT2-3N0-1 located >5 cm from the anal verge with clear mesorectal fascia (MRF). Eligible patients are randomized to selective use of mFOLFOX6 and salvage CRT according to the tumor regression or standard FU-based CRT. Both oncological and functional outcomes are not available yet. The FOWARC trial has offered a glimpse at the answer to this question, where patients assigned to neoadjuvant mFOLFOX 6 without RT had an inferior pCR rate (7%) but comparable downstaging (36%)[29]. Furthermore, the acute toxicity and postoperative morbidity were markedly less developed without radiation. Long-term results of this RT-free strategy are awaited. More recently, a phase-2 trial explored the regimen of 4-6 cycles of FOLFOXIRI (5-FU, oxaliplatin, and irinotecan) without radiation as the neoadjuvant treatment for patients with stage II/III cancer (FORTUNE study)[73]. Of the 80 patients completing at least four cycles of FOLFOXIRI, 12 received salvage CRT or SCRT before surgery. Among patients without RT, the rates of pCR and tumor downstaging were 14% and 41%, respectively.

Organ preservation after complete tumor response

In addition to the idea of omitting RT, much progress in neoadjuvant therapy to better tumor regression has provided alternatives to improve functional outcomes. In the subset of patients who achieve complete tumor response, surgical or nonsurgical approaches that spare the rectum could be applied to avoid unnecessary morbidity and dysfunction.

The nonsurgical management, or so-called watch-and-wait strategy, requires intensive follow-ups to early detect any local or systemic recurrence[74]. Generally, patients with cCR are managed without surgery by regular assessments monthly in the first year, every 2-3 months during the second year, and every 6 months thereafter. Physical and digital examination, proctoscopy, and carcinoembryonic antigen level are necessary for all visits. Pelvic MR and CT scan of the chest and abdomen are recommended to perform every 6 months for the first 2 years and yearly thereafter. This watchful waiting in patients with cCR after CRT was reported to offer comparable oncological outcomes as the radical surgery in patients with pCR (2 year OS, 96% vs 100%; 2 year distant DFS, 88% vs 98%)[75]. The long-term prognosis under strict surveillance was presented as high as 93%-100% for 5 year OS and 85%-92% for 5 year DFS, respectively[36,76]. Local recurrences after "watch-and-wait" management include early regrowth within the first 12 months of follow-up and late recurrence found 12 months afterwards, which together may develop in up to 30% of patients with initial cCR[38,77,78]. However, these local recurrences are usually amenable to salvage therapies, leading to acceptable rates of sphincter preservation and excellent local disease control[77,79]. More recently, a cohort study of 357 patients comparing "watch-and-wait" strategy and radical surgery through propensity-score matching analysis showed no significant differences in 3 year OS (96% vs 87%) and non-regrowth DFS (88% vs 78%), but superiority of watchful waiting in terms of colostomy-free survival (74% vs 47%)[9]. Additionally, this "watch-and-wait" approach has been demonstrated to bring better functional outcomes than transanal local excision (LE) after CRT as organ-preserving strategy[78,80]. More concrete evidence is expected from the International Watch & Wait Database, where all available retrospective and prospective data are collected around the world[81].

Assessment of tumor response is the crucial step to decide an organ-preserving strategy. To accurately identify patients with complete response after neoadjuvant therapy is first challenged by uncertainty of the timing. The optimal interval after CRT might be flexible, as the tumor response varies from patient to patient. Moreover, novel strategies have been developed to improve the tumor regression. Thus a dynamic assessment is needed to differentiate responsive tumors, as well as appropriate candidates for organ preserva-
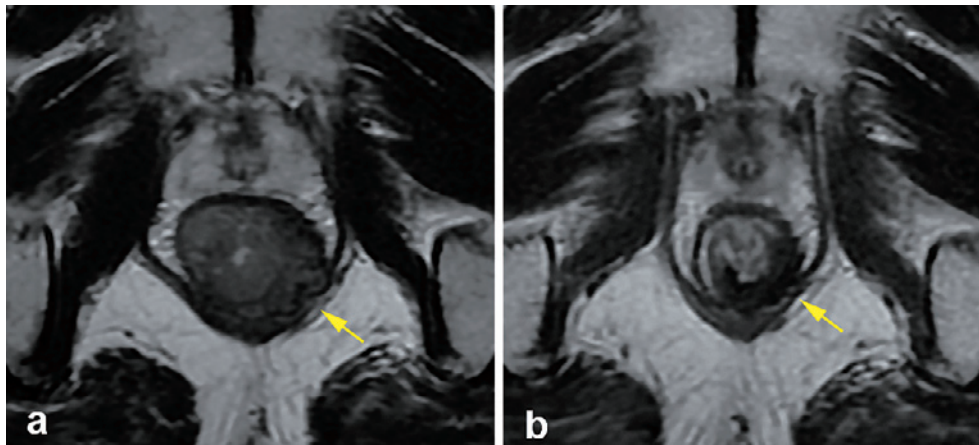
Figure 2. Images showing difference between baseline T4 tumor (a, yellow arrow, left levator ani involved) and post-CRT tumor with complete response (b, yellow arrow, low signal intensity).

tion. Criteria of complete tumor response are also undetermined. Evidence of cCR includes the absence of any irregularity, ulceration, or stenosis during digital examination and proctoscopy[16]. Endoscopic evaluation finds no irregularity or superficial ulcers except for a white flat scar, telangiectasia, or whitening of the mucosa within the area harboring the original tumor. Besides, radiologic assessment should confirm the shrinkage of the tumor and preclude any involvement of mesorectal lymph nodes or vessels (Figure 2)[82]. Although these series of clinical, endoscopic, and radiologic criteria are recommended, the concordance between clinical assessment and pathological confirmation has been found disappointing in several studies. In a retrospective study including 238 operated patients, use of stringent criteria for cCR poorly identified pCR confirmed by radical surgery with a sensitivity of 26%, a specificity of 97%, and a false positive rate of 27%[83]. Similar data were presented in a study assessing cCR using combination of digital examination, proctoscopy, and MRI in 118 patients from a randomized trial[84]. The prediction for pCR with these criteria showed a sensitivity of 18.2%, a specificity of 81.8%, and a false positive rate of 33.3%. The ACOSOG Z6041 trial applied complete disappearance of tumor on endoscopic examination as the predictor of pCR and reported a sensitivity of 85%, a specificity of 67%, and a false positive rate of 33%[85]. Of note, the study enrolled only patients with T2N0 cancer who were more likely to respond to CRT. These data send a message that current criteria of cCR limit the use of nonsurgical management, largely due to the low sensitivity and missed prediction of pCR. Alternative maneuvers are needed to improve the identification of complete response.

Full-thickness LE facilitates pathological assessment of primary tumor response and eliminates potential residual cancer foci, thus being suggested to serve as both a diagnostic and therapeutic approach after neoadjuvant CRT[86,87]. For selected patients who respond well to CRT, LE achieves or-

gan preservation as well as acceptable local recurrence[88]. However, several drawbacks of LE after CRT complicate the decision making. Firstly, LE removes the primary tumor but not mesorectal lymph nodes in most cases. The pathological assessment of tumor response on the basis of LE specimen is actually the pathologically confirmed T stage, with a risk of nodal stage underestimated. Secondly, LE of primary tumor with partial response to CRT is insufficient for oncological outcomes. Data from several prospective trials demonstrated that poor responders with residual ypT2 cancers who insisted LE instead of radical surgery would develop a high rate of local recurrence up to 37%[89,90]. Even R0 resection of the residual cancer cannot eliminate tumor scatter or possible nodal involvement during the incomplete response to CRT[91,92]. Thirdly, there are concerns about the scarring of MRF and extensive regrowth of tumor after LE, which complicate salvage TME and compromise surgical quality by involved circumferential resection margin, leading to an increased risk of failure in local control and sphincter preservation. Finally, surgical morbidity is frequent after LE following RT. The tissue healing is difficult in the irradiated field, resulting in wound separation or dehiscence in 23%-70% of patients undergoing transanal endoscopic microsurgery (TEM) with CRT[93-95]. The subsequent complications, especially anorectal pain, may require hospital readmission in up to 43% of patients[94]. A recent pilot study evaluating SCRT followed by delayed TEM even has to be interrupted by such severe complications[93]. Moreover, anorectal function could be impaired by serious pain and abnormal healing of the separated wound. Some studies of limited sample found that LE following RT achieved better outcomes in early defecation than TME after CRT[96], but equivalent results in anorectal dysfunction as LAR without RT[97]. Altogether, use of LE may be helpful to patients who enjoy complete tumor response, and beneficial to the diagnosis and treatment of tumor near complete response. Salvage TME remains the
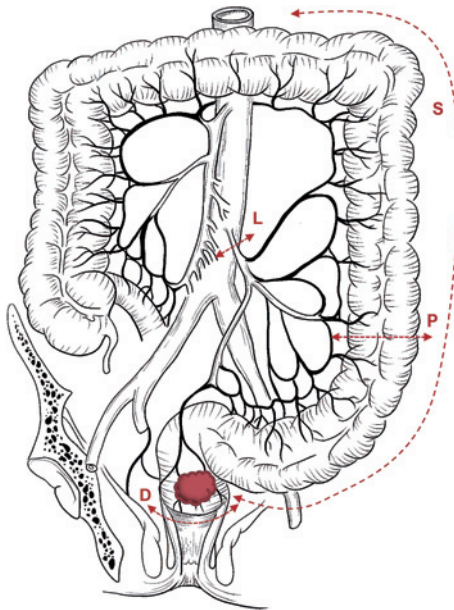
Figure 3. View of the proximally extended resection. D, distal transection; L, ligation of inferior mesenteric artery; P, proximal transection; S, splenic flexure mobilization.

best alternative for patients with incomplete response (ypT1-2) after confirmation by LE.

Radical surgery with modified approaches

Radical surgery, regardless of open, laparoscopic, or robotic techniques, comes with inherent damage to urinary, sexual, and bowel function. The surgical morbidity and requirement for stomas result in additional impairment of QoL. Nonetheless, TME with an intact mesorectum and clear resection margins provides reliable local disease control. Considering the limited rate of complete response after neoadjuvant CRT for advanced rectal cancer, TME with modified approaches to improve functional outcomes is in great demand.

Rectal reconstruction is the pivotal step to determine bowel function after LAR. Apart from end-to-end colorectal or coloanal anastomosis, different approaches to increase colonic reservoir, such as colonic J pouch, side-to-end anastomosis, and transverse coloplasty, have been introduced to improve postoperative function. A meta-analysis incorporating 21 trials of 1636 patients compared the morbidity and functional consequences between these anastomotic methods[10]. The results showed superiority of neorectal reservoir in bowel function up to 12 months postoperatively and no benefit in terms of anastomotic leakage. Similar results were presented in another pooled analysis of 846 patients from 16 trials[98]. Advantage of complicate reconstructions continued for 18 months after surgery, and no difference was found in postoperative complications. In particular, the reservoir construction after RT may confront with considerable technical constraints, including mesorectal edema, tissue fibrosis, and narrow pelvis in male patients. Further investigation is needed in functional outcomes after these modified reconstructions, especially in the context of neoadjuvant CRT.

Another important issue is the management of radiation damage in the pelvis. The recent histopathological research has originally revealed the radiation-induced injury left on surgical margins of LAR after CRT[58]. Routine resection with a 10 cm proximal margin is probably not enough for a healthy anastomosis and favorable bowel function in most cases of TME following CRT. According to the guideline of IMRT contouring for rectal cancer, the superior margin of clinical target volumes reaches as high as the common iliac vessels bifurcation[99]. Therefore, a proximally extended resection has been investigated with an attempt to decrease the occurrence of anastomotic leakage and improve postoperative function (Figure 3)[100].

Summary

Neoadjuvant (chemo) radiotherapy plus high-quality TME is currently the standard of care for locally advanced rectal cancer, but the application is limited by both discontent with systemic disease control and substantial toxicity and dysfunction after surgery. New strategies are developed to improve oncological outcomes, including RT dose escalation, chemotherapy intensification, and CRT with consolidation or full-course chemotherapy. A better tumor regression to the achievement of cCR or even pCR prompts the nonsurgical management with close surveillance, where significant morbidity and dysfunction could be avoided from radical surgery without oncological compromise. Solo chemotherapy is a promising alternative for selected patients, which precludes the RT-related toxicity. TME is still the best decision to provide reliable oncological outcomes for patients with incomplete tumor response after neoadjuvant therapy. In this setting, a proximally extended resection or reconstruction techniques to increase colonic reservoir may benefit functional outcomes.

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