

REVIEW ARTICLE

Surgical issues in locally advanced rectal cancer treated by preoperative chemoradiotherapy

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The standard treatment for patients with locally advanced rectal cancer is preoperative chemoradiotherapy followed by total mesorectal excision. This approach is supported by randomized trials, but there are still many unanswered questions about the multimodal management of rectal cancer. In surgical terms, these include the optimal time interval between completion of chemoradiotherapy and surgery; adequate distal resection margin and circumferential radial margin; sphincter preservation; laparoscopic surgery; and conservative management, including a 'wait and see' policy and local excision. This review considers these controversial issues in preoperative chemoradiotherapy.

Key Words: Rectal cancer, Chemoradiotherapy, Surgical procedures

INTRODUCTION

Radiotherapy, chemotherapy and surgical resection including total mesorectal excision (TME) are the standard components of treatment for patients with locally advanced rectal cancer. The optimum sequence has been investigated in randomized trials, and preoperative chemoradiotherapy (CRT) is the preferred treatment for improving local control. A German trial [1], published in 2004, confirmed that preoperative CRT has significantly lower local failure rates and toxicity rates than postoperative CRT, as well as improved rates of sphincter preservation. These findings led to a change from postoperative to preoperative CRT; preoperative CRT, TME and adjuvant che-

motherapy have become the standard means of care for T3 and/or node-positive rectal cancer. This change has prompted many new questions, including: the optimal interval between the completion of CRT and surgery; adequate distal resection margin (DRM) and circumferential radial margin (CRM); sphincter preservation; laparoscopic surgery; and conservative management including a 'wait and see' policy and local excision. This review discusses the surgical issues of multimodal treatment for patients with locally advanced rectal cancer.

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OPTIMAL TIME INTERVAL BETWEEN COMPLETION OF CHEMORADIOTHERAPY AND SURGERY

Surgery has generally been performed 4 to 8 weeks after conventional CRT is completed. This interval allows the patient to recover from the acute side effects of CRT and adequate time for the tumor to respond to CRT. If the tumor response to CRT is time-dependent, a longer interval between CRT and surgery may result in a better tumor response to CRT, as several retrospective studies have suggested. Tulchinsky et al. [2] reported that patients operated on more than 7 weeks after CRT had a pathologic complete regression (pCR) rate of 35%, compared with 17% for patients operated on less than 7 weeks after CRT ($P = 0.03$). Kalady et al. [3] reported a 31% pCR rate in patients operated on more than 8 weeks after CRT compared with 16% in patients operated on less than 8 weeks after CRT. Moore et al. [4] suggested that a longer interval between CRT and surgery was associated with an increased pCR rate (19% pCR rate in patients operated on more than 44 days after CRT, compared with 12% in patients operated on less than 44 days after CRT), but the effect obtained was not statistically significant. However, other studies have observed no difference in pCR rates for longer intervals between CRT and surgery [5,6]. Recently, the Timing of Rectal Cancer Response to Chemoradiation Consortium reported preliminary results from a prospective, multi-center, phase II clinical trial investigating extending the interval between CRT and surgery [7]. After conventional CRT using 5-Fluorouracil and radiation for 5 to 6 weeks, the patients of study group 1 (SG1, $n = 60$) underwent TME 6 weeks later, and patients of study group 2 (SG2, $n = 67$) who showed a clinical response 4 weeks after CRT received two cycles of modified FOLFOX-6 followed by TME 3 to 5 weeks later. The average times between CRT and surgery were 6 weeks (SG1) and 11 weeks (SG2), and the rates of pCR were 18% (SG1) and 25% (SG2, $P = 0.0217$). Based on these results, the Consortium suggested that adding chemotherapy after CRT and extending the interval between CRT and surgery increases the pCR rate.

Traditionally, surgeons have been reluctant to postpone surgery for more than 6 to 8 weeks after CRT, because of

the concern that postradiotherapy fibrosis may increase the difficulty of the TME and increase the risk of postoperative complications. In addition, a longer interval might allow the tumor to spread, which could ultimately reduce survival rates.

The Timing of Rectal Cancer Response to Chemoradiation Consortium reported more pelvic fibrosis in patients operated on 11 weeks after CRT (score 4.0) than after 6 weeks (score 2.4) ($P = 0.0003$) [7]. However, the increase in fibrosis did not significantly increase the technical difficulty of the operation ($P = 0.2220$) and did not increase the risk of postoperative complications [7]. Several previous studies also reported that increasing the interval between the completion of CRT and surgery did not appear to increase postoperative morbidity [2,4-6,8-12].

The impact of delaying surgery on the oncological outcome is an important consideration. Few studies have examined long-term data on the interval between CRT and surgery. Glehen et al. [13] reported the long-term results of the Lyons R90-01 trial, which examined outcomes after short (less than 2 weeks) and longer intervals (6 to 8 weeks) after preoperative radiotherapy (RT) (39 Gy in 13 fractions). The study found similar overall survival (OS) and local recurrence rates for the two groups during a 6.3-year median follow-up period, and suggested that delaying surgery was not detrimental to survival. Consistent with the Lyons trial, several studies [6,7] reported that a longer interval between preoperative RT or CRT and surgery did not lead to a worse outcome than a shorter interval. In contrast, other groups reported that delayed surgery did have a negative impact on survival. Supiot et al. [14] found that an interval of more than 16 weeks between diagnosis and surgery could reduce OS rates for patients treated with preoperative radiation. They concluded that surgery should be performed shortly after irradiation is completed.

Thus the optimal interval between CRT and surgery remains uncertain. Investigators in the United Kingdom are currently evaluating an interval of 8 to 12 weeks between completion of CRT and surgery (NCT01037049 trial), compared with the standard 4 to 6 weeks. Although longer intervals may be associated with a greater response to CRT, this must be weighed against the potential effects of allowing tumors to continue to spread, and the resulting con-

cern about impaired surgical outcomes.

ADEQUATE DISTAL RESECTION AND CIRCUMFERENTIAL RADIAL MARGIN

The DRM affects both local recurrence and the feasibility of sphincter-preserving surgery for rectal cancer. The current National Comprehensive Cancer Network (NCCN) guidelines recommend a DRM of 4 to 5 cm for an adequate mesorectal excision and 1 to 2 cm for TME in patients with distal (<5 cm from the anal verge) rectal cancers. They also suggest that the DRM should be confirmed to be tumor-free by frozen section [15]. These suggestions are based on the findings that distal mesorectal spread is limited to 4 to 5 cm from the distal tumor edge [16,17], and distal intramural or extrarectal spread, if present, is limited to within 2 cm in 95% of all patients [18,19].

The 2 cm rule is supported by several studies on the effect of the DRM on oncological outcomes. Pollett and Nicholls [18] divided 334 rectal cancer patients who underwent curative resection into three groups according to the length of the DRM: ≤ 2 cm, >2 to <5 cm, and ≥ 5 cm. They found that these three groups had similar results for local recurrence and OS. Although some investigators have suggested a DRM of 1 cm [20], such a short DRM is not acceptable in locally advanced rectal cancer because the extent of distal spread is associated with a tumor stage [21].

However, distal tumor spread can be pathologically cleared by preoperative CRT, and a clear DRM of 1 cm has been suggested to be oncologically adequate in patients who receive preoperative CRT [22]. This suggestion is supported by a prospective study by Guillem et al. [23], who analyzed distal intramural spread in 109 rectal cancer specimens after preoperative CRT and TME by comprehensive whole-mount pathology. Only two specimens (1.8%) had intramural extensions beyond tumor edges measuring less than 0.95 cm. The main problem is that the length of the DRM depends on the measurement method. The various measurement methods for DRM must be compared to determine an oncologically safe DRM.

The status of the CRM has a substantial impact on local

recurrence rates [15,24-26] and has been found to be an acceptable surrogate endpoint for local recurrence and disease-free survival (DFS) [27]. NCCN guidelines suggest that a positive CRM is defined as tumor ≤ 1 mm from the margin [15] and Folkesson et al. [28] reported that the local recurrence rate was 22% when the CRM was involved and 5% when the CRM was not involved (> 1 mm).

The CRM issue in rectal cancer is closely associated with the location of the tumor. The risk of an involved CRM is higher for low rectal cancers because the mesorectum tapers as it approaches the levator muscles. The Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study [29] reported surgical outcomes in 153 patients with low rectal cancers and found that 31.9% of abdominoperineal resection (APR) specimens had involved CRM, compared with 12% of low anterior resections. They also reported that the quality of the mesorectal specimens was worse in patients undergoing APR (complete TME: 30.6% in APR vs. 75.3% in anterior resection). Therefore, the European Extralevator Abdominoperineal Excision Study Group suggested a wider perineal resection to address the problem of conventional APR and reported the results of 176 patients who had undergone extralevator APR. They confirmed that removing additional tissue reduced CRM involvement (from 49.6% to 20.3%, $P < 0.001$) [30].

SPHINCTER PRESERVATION

One aim of preoperative CRT followed by surgical resection is tumor downstaging and reducing tumor volume, which may make sphincter-preserving surgery possible. Two randomized trials [1,31] of preoperative and postoperative CRT for clinically resectable locally advanced rectal cancer reported opposing results. In a German trial [1], among 194 patients assessed by the surgeon before treatment as requiring APR, there was a significant improvement in sphincter preservation with preoperative therapy (39% with preoperative therapy; 20% with postoperative treatment; $P = 0.004$). However, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial [31], based on a prospective assess-

ment by the operating surgeon, there was no improvement in sphincter preservation (47.8% of the preoperative patients; 39.2% of the postoperative patients; $P = 0.227$). The results of the NSABP R-03 trial should be interpreted with caution, however, as they were obtained from only 267 of the 900 intended patients. The positive findings from the German trial were based on results from a sufficient number of patients, and the possibility of improved sphincter preservation by preoperative CRT remains one of the important benefits of this approach. Weiser et al. [32] also reported the benefit of preoperative CRT for sphincter preservation. They performed a retrospective analysis of 148 rectal cancer patients (within 6 cm of the anal verge) and concluded that preoperative CRT improved sphincter-preserving surgery in addition to intersphincteric resection.

However, the link between preoperative CRT and improved sphincter-preserving surgery is complex. First, the reduction in tumor volume is not correlated with ypT and/or ypN stage [33]. Secondly, the location of the tumor is the main determining factor for sphincter-preserving surgery. If the tumor invades the anorectum directly, sphincter preservation is unlikely, even with significant tumor regression. The surgeon's experience and skill also affect the outcome of sphincter-preserving surgery. The noticeable improvement in this type of surgery in recent years is mainly due to technical and conceptual improvements. Some investigators have reported that the significant improvement in sphincter-preserving surgery in rectal cancer 3 to 5 cm from the anal verge is due to the introduction of double stapling and coloanal anastomosis techniques [34].

There are two meta-analyses to determine whether preoperative radiotherapy improves the outcome for patients with localized resectable rectal cancer. Wong et al. [35] analyzed the results of 19 trials comparing preoperative radiotherapy with surgery alone, and reported that the evidence did not show any sphincter-preserving benefit of combined CRT or selective postoperative radiotherapy. The pooled odds ratio for preoperative radiotherapy was 0.94 (95% confidence interval, 0.88 to 1.04), which was not statistically significant. However, the data were borderline in homogeneity ($P = 0.05$), suggesting there were var-

iations in the magnitude of effect across the studies. In a recent review that analyzed 17 randomized trials, the authors concluded that none of the neoadjuvant treatments tested was able to demonstrate an increase in the rate of sphincter-preserving surgery [36]. However, these two meta-analyses did not consider the effect of conservative management (transanal local excision or close observation for good responder to CRT) on the rate of sphincter-preserving surgery. Recently, several clinical trials have found local excision to be a promising surgical treatment after preoperative CRT. If the oncological safety of conservative management after preoperative CRT for low-lying rectal cancer, where conventional APR is inevitable, is established, the benefit of improved sphincter preservation from preoperative CRT should be reevaluated.

LAPAROSCOPIC SURGERY

Laparoscopic procedures for rectal cancer are technically demanding because TME and autonomic nerve preservation are prerequisites for functional and oncological safety. Although the results are still a matter for debate, the use of laparoscopy for rectal cancer has increased because of its short-term feasibility, safety, and oncological evidences [37-43].

However, there is insufficient surgical evidence for laparoscopic resection for rectal cancer treated by preoperative CRT. Few studies have compared the short-term outcomes of laparoscopy with outcomes from open surgery after preoperative CRT in mid or low rectal cancer [44]. Only one randomized trial has demonstrated the safety of laparoscopic surgery after preoperative CRT. The comparison of open versus laparoscopic surgery for mid and low rectal cancer after neoadjuvant chemoradiotherapy (COREAN) trial [45] compared open surgery ($n = 170$) with laparoscopic surgery ($n = 170$) for mid or low rectal cancer after preoperative CRT. The results shows that laparoscopic surgery is feasible and does not increase short-term oncological risks, which are predicted by CRM positivity (open 4.1% vs. laparoscopic 2.9%) and macroscopic quality of TME specimens (complete TME: open 74.7% vs. laparoscopic 72.4%), or the number of harvested

lymph nodes (open 18 vs. laparoscopic 17), which can be associated with long term oncological outcomes and does not increase morbidity (open 23.5% vs. laparoscopic 21.2%) compared with open surgery. The findings also suggested that laparoscopic surgery resulted in a better quality of life for up to 3 months after surgery. However, the long-term oncological outcome needs to be established, taking into account the inherent differences of TRG and yp-stage between the two groups. The feasibility and oncological safety of the laparoscopic approach for rectal cancer patients treated by preoperative CRT needs to be evaluated further. Recently, robot-assisted rectal cancer surgery has shown that it is possible to overcome the technical limitations of laparoscopy [46], but this also needs further evaluation.

CONSERVATIVE MANAGEMENT

Surgical resection of the rectum may be associated with significant morbidity with permanent stoma construction [47]. Furthermore, significant anorectal dysfunction (restricted social lives or deteriorating quality of life) occurs in some rectal cancer patients who have been treated by preoperative RT followed by radical surgery [48-50]. Although the standard management of locally advanced rectal cancer treated by preoperative CRT is surgical resection by APR, or sphincter-preserving low anterior resection where it is possible, conservative management (local excision or close observation) has been used in individual cases (such as patients' refusal of radical surgery, severe comorbidities, or clinical trials).

Tumor downstaging after preoperative CRT may be able to eradicate all viable tumor cells in the primary rectal tumor and regional lymph nodes; complete regression of the tumor occurred in up to 30% of patients. Some investigators examined the results of performing a transanal local excision or close observation, without radical surgery, to avoid possible morbidities such as permanent stoma formation and functional impairments.

No results from randomized trials with close observation are available. Habr-Gama et al. [51] questioned the value of radical surgery in patients with biopsy-pro-

ven complete responses in 1998, and reported a single-center experience of non-operative treatment in clinical complete response patients in 2004 [52]. The long-term outcome of the observation group (5 year OS 100%, DFS 92%) was similar to that of the resection group (5 year OS 88%, DFS 83%) with histologic complete response, indicating that clinical complete responses in selected patients often corresponded to pathological complete responses. However, other investigators have been unable to reproduce these results. Hughes et al. [53] reported 60% intrapelvic recurrence rates in 10 cases with clinical complete response and concluded that a 'wait and see' policy could not be justified in T3/4 rectal cancers after CRT. Nakagawa et al. [54] also reported high (80%) local recurrence rates in 10 cases with clinical complete response and suggested that an exclusive CRT approach is not safe for treating patients with low infiltrative rectal carcinoma. Another difficulty with the observation policy is in determining a clinical complete response. After CRT, ycT and ycN categories should be evaluated to determine the tumor response to CRT. These parameters can be evaluated by digital examination, proctoscopy, abdominal CT scan or endorectal ultrasound, magnetic resonance imaging and fluorodeoxyglucose positron emission tomography. Glynne-Jones et al. [55] reviewed 218 phase I/II and 28 phase III trials of preoperative radiotherapy or CRT. They concluded that a clinical and/or radiological response does not sufficiently correlate with the pathologic response to recommend a 'wait and see' approach to surgery following preoperative therapy. As some patients with clinical complete response have a microscopic residual tumor at resection, surgery remains the standard approach after preoperative CRT, even in patients who appear to have a clinical complete response.

Local excision of rectal cancer in patients with a good clinical response after CRT has been a promising surgical option. Several clinical trials reported that long-term outcomes in highly selected patients do not differ significantly from those of transabdominal techniques. Hingorani et al. [56] analyzed the use of local excision after CRT in 10 retrospective, one single-arm prospective, and one randomized series, and concluded that local excision may be appropriate for selected patients who have a good clin-

ical response after CRT. A full thickness local excision can be performed easily with very low morbidity rates, preserving sexual and urinary function, sparing rectal function, and, in cases of very low rectal cancer, avoiding permanent stoma.

However, local excision after CRT has not gained acceptance because of concern about local recurrence, as there has been no mesorectal lymphadenectomy and the lymph node stage is undefined. Local excision should be performed only in cases of clinical complete regression without mesorectal lymph node involvement. However, as mentioned before, the clinical and pathological responses do not always agree. When nodal involvement is understaged and patients undergo local excision, the prognosis becomes worse.

Recently, the American College of Surgeons Oncology Group has completed the Z6041 phase II trial of patients with clinical T2N0 rectal cancer who received preoperative CRT (total dose 54 Gy) with capecitabine and oxaliplatin followed by transanal local excision 6 weeks after completion of CRT [57]. Of 77 patients who underwent local excision, 34 achieved a pCR (44%), 49 (64%) had ypT0-1, and 4 (5%) had ypT3 tumors. All but one had negative margins. Acute toxicity of at least grade 3 during CRT occurred in 39% of the patients, and rectal pain was the most common postoperative complication. Clearly, longer follow-up is needed to assess the oncologic outcome. After acceptance for oncologic safety of the Z6051 trial, the next step could be phase II nonrandomized trials in patients with cT3 rectal cancer.

ISSUES FOR THE FUTURE

Multimodal treatment for locally advanced rectal cancer patients has evolved, and must be further optimized. Important issues are testing for response or nonresponse to CRT before administering CRT, and accurate evaluation of tumor responsiveness or nodal involvement in the mesorectum with improved imaging. These clinicopathologic and/or molecular predictors as well as accurate evaluators (imaging or nomograms) should be an integral part of the multimodal treatment of locally advanced rectal cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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