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Perspective

Advances for achieving a pathological complete response for rectal cancer after neoadjuvant therapy

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Abstract

Neoadjuvant therapy has become the standard of care for locally advanced mid-low rectal cancer. Pathological complete response (pCR) can be achieved in 12%−38% of patients. Patients with pCR have the most favorable long-term outcomes. Intensifying neoadjuvant therapy and extending the interval between termination of neoadjuvant treatment and surgery may increase the pCR rate. Growing evidence has raised the issue of whether local excision or observation rather than radical surgery is an alternative for patients who achieve a clinical complete response after neoadjuvant therapy. Herein, we highlight many of the advances and resultant controversies that are likely to dominate the research agenda for pCR of rectal cancer in the modern era.

Keywords: Rectal cancer; Neoadjuvant therapy; Pathological complete response; Local excision; Wait and see

Introduction

Multidisciplinary therapy is the basic principle of rectal cancer treatment, and radical surgery remains the main treatment. For early tumors, radical total mesorectal excision (TME) is curative. However, for locally advanced low rectal cancer (T3/T4 or N+) with a relatively high risk of locoregional recurrence, neoadjuvant therapy followed by TME has become the standard of care in order to downstage the tumor, thereby facilitating dissection and improving surgical outcomes.[1] Tumor regression after chemoradiotherapy (CRT) is observed in most patients, with 12%−38% cases showing a pathological complete response (pCR) in postoperative specimens.[2−5] The predictive factors of pCR include the primary tumor size, histological type, pretreatment clinical stage, neoadjuvant therapy regimens, and interval between neoadjuvant therapy and surgery.[6−8] Achievement of pCR after neoadjuvant

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CRT is associated with greatly improved cancer outcomes and significantly decreased local recurrence (LR) in locally advanced rectal cancer (LARC).[9,10] Recently, it has been suggested that radical surgery should be avoided in patients who achieve a clinical complete response (cCR). Selected patients may benefit from the management of local excision (LE) or simple observation ("wait and see" or "wait and watch" strategy), improving the possibility of organ preservation with comparable survival.[11−14] Here, the latest advancements in clinical research on pCR after neoadjuvant therapy are reviewed, focusing on current imaging, predictive factors, prognosis and management. We highlight many of the advances and resultant controversies that are likely to dominate the research agenda for pCR of rectal cancer in the modern era.

Restaging after neoadjuvant therapy for rectal cancer

Implementation of neoadjuvant therapy requires an accurate staging to identify patients who would benefit from such treatment. Current imaging techniques have been reported to be highly accurate in the primary staging of rectal cancer. However, a neoadjuvant therapy course induces deep modifications of cancer tissue and surrounding structures such as fibrosis with mucin pools, deep stroma alteration, bowel wall thickening, muscle disarrangement, tumor necrosis, calcification, and inflammatory infiltration. As a result, the same imaging techniques, when used for restaging, are much less accurate. Sensitivity, specificity, and accuracy of computed tomography (CT), endorectal ultrasonography (EUS), and magnetic resonance imaging (MRI) to preoperatively determine locoregional neoplastic extension are suboptimal for this purpose.

The accuracy of CT in predicting T stage after a neoadjuvant therapy course is still controversial in the literature.[15,16] CT scanning is commonly considered an unreliable restaging technique to assess pCR.[17] In a study conducted by Huh et al[18] in 80 patients, the retrospectively analyzed CT scans were unable to predict pCR in any patient. Restaging lymph nodes after a neoadjuvant therapy course could also be more complex because radiotherapy has the ability to reshape and modify the size and texture of the nodes. In terms of nodal involvement, CT has an accuracy of 82% by using a cutoff of 10 mm.[16] On the contrary, in a 5-mm cutoff setting, the accuracy has been reported to be 62%.[17]

The assessment of rectal tumor by means of EUS is based on the evaluation of depth of invasion through the five layers of the bowel wall. The accuracy of EUS ranged from 27% to 72% in T restaging but only 0%−60% in correctly diagnosing ypT0.[19] Its accuracy in restaging lymph nodal involvement ranged between 39% and 83%. The accuracy of EUS is insufficient in detecting which tumors show T0N0 after neoadjuvant treatment.

MRI currently plays a crucial role in the primary staging of rectal cancer by guiding therapeutic management.[20] The sensitivity of MRI for T stage was 87%, and its specificity was 75% in the primary staging of rectal cancer.[21] Diffusion-weighted MRI, especially at high *b* values, would be effective for the prediction of treatment outcome and early detection of tumor response. The addition of diffusion-weighted imaging to standard rectal MRI improves the selection of complete responders after chemoradiation.[22,23] Dynamic contrast-enhanced magnetic resonance imaging is reported to have a sensitivity of 100% for distinguishing complete and incomplete responses.[24] Nodal staging by using MRI usually relies on size criteria but was a poor predictor of nodal status. Using 5 mm (any axis) as a cutoff for an abnormally sized lymph node has proven to provide a sensitivity of 66% and a specificity of 76% to predict malignant involvement.[25]

Management of cCR

Contemporary management of LARC involves preoperative CRT, followed by surgery and then adjuvant systemic chemotherapy. Despite various degrees of tumor response, radical resection of the primary tumor and draining lymph nodes remain the standard recommendation. Most published studies reported a favorable prognosis in patients who achieved a pCR after neoadjuvant therapy followed by TME.[9,26,27] Aggressive TME surgery is a significant associated risk factor of morbidity, including anastomotic leakage, pelvic automatic nerve injury, and mortality.[27−32] Moreover, a proportion of patients who underwent rectal cancer surgery will require either a temporary or permanent stoma. It has been suggested that radical surgery be omitted in patients with cCR, especially in patients with distal tumors, avoiding a permanent stoma.[11,12]

LE may offer the possibility of organ preservation for the management of selected patients after neoadjuvant CRT. Callender et al[33] reported that full-thickness LE offers a comparable local control, disease-free survival (DFS), and overall survival (OS) to that achieved with proctectomy and TME. LE also

enables primary tumor staging with 100% accuracy after neoadjuvant therapy. In case of poor response or non-pCR, a salvage TME surgery could be performed timely.[34]

The non-surgical, observation-only replacement therapy ("wait and see") was first introduced by Habr-Gama et al.[11] In a prospectively observed cohort of patients with a cCR, no initial surgical intervention was performed. During almost 5 years of follow-up, they reported LR, DFS, and OS rates comparable to those in patients who underwent immediate low anterior or abdominoperineal resection with TME. None of the patients developed pelvic LR. The reported 5-year DFS of 71 cCR patients was 92%, compared with the 83% for patients with radical surgery-confirmed pCR ($P = 0.09$). Maas et al[14] proposed a strict selection criterion for the wait-and-see policy, not only confirming that the oncological outcome after observation was comparable with that in patients who achieved a pCR after radical excision but also evaluating bowel function. Patients who underwent observation had better functional outcomes than those who received surgery. The difference was larger in terms of control over flatus and the change in bowel habits, since all the patients with a pCR after surgery had changed bowel habits.

Two key points need to be clarified in investigating whether LE or "wait and see" could be a valid alternative to radical surgery. First, a significant correlation was found between cCR and pCR. Hiotis et al[35] performed a retrospective review of the clinical and pathological characteristics of 488 patients from the Memorial Sloan-Kettering Prospective Colorectal Database. This study demonstrated a 19% cCR rate with preoperative therapy and a 10% pCR rate among all patients. The pCR rate among the clinical complete responders was 25%, and most (75%) of the cCR patients had persistent foci of tumor that was not detectable on preoperative examination or colonoscopy. Smith et al[36] retrospectively assessed the morphological and histological features of residual tumor and found that 61.3% (19/31) of patients with a pCR had evidence of a residual mucosal abnormality consistent with an incomplete clinical response. Thus, it is unreliable to predict pCR simply based on the absence of clinically palpable or visible tumor after neoadjuvant therapy. Second, the rate of lymph node metastasis in ypT0 patients should be low enough. Coco et al[37] reported that the rate correlated with ypT stage, with 1.8% for ypT0 cases and 6.3% for ypT1 cases. In a literature review, Kundel et al[38] summarized the rate of involved lymph nodes in ypT0 patients to range from 0% to 17%, with an average rate of lymph node involvement of 5%.

Therefore, owing to the accuracy limitation, modern imaging techniques are unreliable in restaging rectal cancer after CRT. A negative preoperative biopsy result after a near-complete clinical response should not be considered sufficient for avoiding a radical resection.[39] With a sensitivity of 50% and negative predictive value of 11%, the accuracy of a simple forceps biopsy for predicting pathological response after neoadjuvant CRT was only 53%, which prevents the uncritical extrapolation of LE or "wait and see" as a routine therapeutic option for clinically proved complete responders, except in selected patients with a strong will for sphincter-saving or could not tolerate radical surgery because of poor physical condition.

Predictive factors of pCR

As patients with a pCR have better long-term outcomes than those without a pCR, in recent years, many trials have used pCR as a surrogate end-point for long-term outcomes such as DFS or even OS.[40] Complete regression has been reported in 12–38% of patients.[2–5,41–43] Therefore, improving the rate of pCR is also a major task in neoadjuvant therapy for rectal cancer. It is commonly believed that different neoadjuvant therapeutic regimens and intervals between neoadjuvant CRT and surgery significantly affect the pCR rate. Other factors that predict a pCR after neoadjuvant treatment of rectal cancers include absence of circumferential involvement and signet ring cell histology, primary tumor size, histological type, and pretreatment clinical stage.[6–8]

Neoadjuvant therapy regimen and pCR

Long-course (LC) preoperative CRT has been widely practiced in the last two decades.[27] The Swedish Rectal Cancer Trial 3 demonstrated that short-course (SC) preoperative radiotherapy reduced the risk of LR by half.[44] To date, only 2 randomized trials (Polish and Australian randomized studies) have directly compared short- and long-course therapies with delayed surgery in resectable rectal cancer.[45,46]

The Polish study compared short- and long-course preoperative pelvic radiotherapies for T3/T4 mid to low rectal cancer, and found higher rates of pCR in the LC (16%) than in the SC (1%) group.[45] In the Australian randomized trial for clinical stage T3 rectal cancer that compared SC radiotherapy with LC-CRT, no differences in distant recurrence rates

(27% *vs.* 30%, $P = 0.92$) and OS (74% *vs.* 70%, $P = 0.62$) were found. In particular, 24 LC patients (15%) had ypT0 (pCR) as compared with only 2 SC patients (1%).[46]

The administration of chemotherapy before neoadjuvant CRT has the theoretical advantages of downstaging a locally advanced tumor, eliminating micrometastatic disease, and improving tolerance to chemotherapy when compared with its administration in the adjuvant setting. Short-course radiotherapy does not include administration of sensitizing chemotherapy. Long-course radiotherapy includes administration of sensitizing therapy, most commonly 5-fluorouracil (5-FU). Two randomized controlled trials, EORTC 22921 and FFCD 9203, showed that the addition of fluorouracil to radiotherapy significantly increased the pCR rate as compared with radiotherapy alone.[47,48] Gérard et al[48] compared neoadjuvant radiotherapy plus capecitabine with dose-intensified radiotherapy plus capecitabine and oxaliplatin in 598 randomly assigned patients and concluded that the addition of oxaliplatin to radiotherapy did not significantly increase the tumor response rate (13.9% *vs.* 19.2%, $P = 0.09$). Similar results were also obtained in the STAR-01 trial.[49] Mohiuddin et al[50] reported that even in fixed rectal cancers, continuous infusion of 5-FU and a preoperative radiation dose of 5500 cGy or higher could achieve a pCR rate of 44%. Further analysis demonstrated that in patients treated with high-dose radiation greater than 5500 cGy, a significantly higher pCR (67%) was observed in patients who received continuous venous infusion, but none of the patients with bolus 5-FU achieved pCR ($P = 0.017$).[50]

In a recent study reported by Schrag et al,[51] 8 (25%) of 32 patients with clinical stage II to III rectal cancer who received 6 cycles of FOLFOX (5-FU, leucovorin, and oxaliplatin) with bevacizumab achieved pCR. This finding demonstrated that a neoadjuvant systemic therapy without routine use of pelvic radiation could be delivered without apparent compromise of either short- or long-term outcomes in carefully staged patients with rectal cancer.

In an attempt to increase pCR rates and reduce local and distant recurrence, several strategies have been evaluated, including the addition of other chemotherapeutic agents and targeted therapies to 5-FU and radiation, as well as induction chemotherapy before concurrent CRT. Crane et al[52] treated patients with clinically staged T3N1 ($n = 20$) or T3N0 ($n = 5$) rectal cancer by administering neoadjuvant therapy with radiotherapy (50.4 Gy/28F), bevacizumab every 2 weeks (3 doses of 5 mg/kg), and capecitabine (900 mg/m^2 orally twice daily only on days of radiation), followed by TME resection. In their study, they observed that 8 (32%) of 25 patients had a pCR, confirming the feasibility of neoadjuvant chemotherapy with XELOX plus bevacizumab. Dipetrillo et al[53] reported treating patients with rectal cancer by using an induction regimen consisting of bevacizumab plus modified infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX6) followed by concurrent bevacizumab, oxaliplatin, continuous infusion of 5-FU and radiation. Five (20%) of 25 patients had a pCR. The addition of bevacizumab to neoadjuvant CRT resulted in an encouraging pCR rate. However, these studies were limited by the single-arm analysis design without a control group.

Induction chemotherapy has been suggested to affect preoperative CRT efficacy in LARC. In a randomized multicenter phase II study conducted by Marechal et al,[3] patients with T2−T4/N+ rectal adenocarcinoma were randomly assigned to arm A—preoperative CRT with 5-FU continuous infusion followed by surgery—or arm B—induction oxaliplatin, folinic acid, and 5-FU followed by CRT and surgery. No statistically significant differences in pCR (28% *vs.* 26%) were found. In another multicenter phase II trial, patients in group 1 had TME 6−8 weeks after CRT. The patients in group 2−4 received additional 2, 4, or 6 cycles of mFOLFOX6. A comparison between patients who received 6 cycles of mFOLFOX6 and those who received the standard neoadjuvant CRT showed a significant difference in pCR rate (38% *vs.* 18%, $P = 0.011$). This strategy is being tested in phase III clinical trials.[54]

In the FOWARC study from China, 495 patients with rectal cancer within 12 cm from the anal verge, clinical stage II or III, were randomly assigned to receive 5-FU with radiotherapy (control arm), mFOLFOX6 with radiotherapy (FOLFOX-RT arm), or 4−6 cycles of mFOLFOX6 alone (FOLFOX arm). The pCR rates were 12.5%, 31.3%, and 7.4% in the control, FOLFOX-RT, and FOLFOX arms, respectively ($P = 0.001$). mFOLFOX6 concurrent with RT resulted in a higher pCR rate.[55]

The interval between neoadjuvant therapy and surgery

It is recommended by the National Comprehensive Cancer Network (NCCN) guidelines that surgery should be implemented within 5−10 weeks after neoadjuvant therapy. During this interval, which

allows for tumor regression but not extensive fibrosis, patients could recover from any treatment-related toxicity and be relieved of local acute inflammatory response to radiotherapy. Studies have indicated that extending the interval between CRT and surgery may increase the proportion of patients who achieve a pCR. Wolthuis et al[56] showed a significantly higher pCR rate after a longer interval (over 7 weeks, 28%) than after a shorter interval (no more than 7 weeks, 16%; $P = 0.006$). In a meta-analysis, Petrelli et al[8] systematically reviewed 13 prospective or retrospective studies, including 3584 patients, and found that a longer waiting interval (more than the classic 6–8 weeks) from the end of preoperative CRT increased the rate of pCR by 6% in rectal cancer, without compromising similar outcomes and complication rates. Although longer intervals may result in favorable pathological findings, it is unclear whether this translates into clinical benefits.[57] In a recently published study, compared with short interval (2 weeks), longer interval (6–8 weeks) was significantly associated with pCR (26% *vs*. 10.3%, $P = 0.015$), but had no impact on survival.[58]

Delayed surgery may induce pelvic fibrosis and increase the technical difficulty of the operation and the risk of surgical complications and locoregional recurrence.[59] For now, whether delayed surgery after neoadjuvant CRT could offer clear benefits in terms of pCR remains unclear. Grimminger et al[60] suggested that pretreatment of intratumoral epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) mRNA expression levels, as well as *KRAS* mutation status, were predictive markers of pathological response to neoadjuvant cetuximab-based chemoradiation in LARC. In the future, for the proper selection of patients who will benefit from neoadjuvant therapy, predictive molecular markers should be identified.

Adjuvant chemotherapy for pCR

According to the latest NCCN guideline, adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer who have undergone neoadjuvant CRT/surgery regardless of the surgical pathological results. However, when no viable tumor is identified in postoperative specimens, the benefit of adjuvant chemotherapy is much less clear. Complete response to neoadjuvant CRT may indicate tumor chemosensitivity and is an important biomarker of long-term outcome.[57] Geva et al[61] analyzed the data of 260 patients with rectal cancer who had been treated with neoadjuvant chemotherapy. Of the patients, 54 were found to have achieved pCR. They suggested that adjuvant chemotherapy played no part in the DFS and OS of pCR patients. Kiran et al[62] even challenged the routine use of adjuvant chemotherapy for patients whose cancers have no node involvement. At present, the comprehensive multidisciplinary treatment strategy for rectal cancer needs to be balanced between inadequate treatment and overtreatment.

Conclusion

Pathological complete response after neoadjuvant therapy for rectal cancer is associated with significantly improved long-term outcomes. Intensified neoadjuvant therapy and delayed surgery are likely to increase the pCR rate. Owing to the limited accuracy of clinical imaging in predicting pCR, radical surgery remains the standard of care for patients downstaged by neoadjuvant therapy. LE or the "wait and see" strategy should be recommended with caution in selected cCR patients who have a strong will for sphincter-saving or could not tolerate radical surgery.

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