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REVIEW

Treatment of locally advanced rectal cancer: Controversies and questions

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Abstract

Rectal cancers extending through the rectal wall, or involving locoregional lymph nodes (T3/4 or N1/2), have been more difficult to cure. The confines of the bony pelvis and the necessity of preserving the autonomic nerves makes surgical extirpation challenging, which accounts for the high rates of local and distant relapse in this setting. Combined multimodality treatment for rectal cancer stage Ⅱ and Ⅲ was recommended from National Institute of Health consensus. Neoadjuvant chemoradiation using fluoropyrimidine-based regimen prior to surgical resection has emerged as the standard of care in the United States. Optimal time of surgery after neoadjuvant treatment remained unclear and prospective randomized controlled trial is ongoing. Traditionally, 6-8 wk waiting period was commonly used. The accuracy of studies attempting to determine tumor complete response remains problematic. Currently, surgery remains the standard of care for rectal cancer patients following neoadjuvant chemoradiation, whereas observational management is still investigational. In this article, we outline trends and controversies associated with optimal pre-treatment staging, neoadjuvant therapies, surgery, and adjuvant therapy.

Key words: Rectal cancer; Neoadjuvant chemoradiation; Response; Treatment; Staging; Recurrence

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INTRODUCTION

The mainstay of treatment for colorectal cancer is surgery. Complete, margin-negative resection confers the greatest chance for cure. However, chemotherapy and radiation have important roles in assuring long-term, recurrence-free survival. Colon cancer and extraperitoneal rectal cancers (lesions above the anterior peritoneal reflection, or 12-15 cm from the anal verge) are generally treated with surgery followed by adjuvant chemotherapy; these patients are believed to be at high risk for harboring micrometastasis and, therefore, of developing of recurrent disease. Mid to low rectal cancers lying below

the anterior peritoneal reflection and extending through the rectal wall, or involving locoregional lymph nodes (T3/4 or N1/2), have historically been more difficult to cure. The confines of the bony pelvis and the necessity of preserving the autonomic nerves makes surgical extirpation challenging, which accounts for the high rates of local and distant relapse in this setting. The Gastrointestinal tumor study group and National surgical adjuvant breast and bowel project trials demonstrated that chemoradiotherapy following surgical resection could reduce local recurrence from 55% to 33%, with significantly prolonged disease-free survival (DFS)[1,2]. This was the basis for the National Institute of Health consensus statement in 1990 recommending combined modality therapy for Stage Ⅱ and Ⅲ rectal cancer[3]. In the 20 years since, there have been considerable advances in treatment.

We will outline current trends and controversies in the treatment of locally advanced rectal cancer. The topics to be covered include staging, neoadjuvant therapies, surgery, and adjuvant therapy.

OPTIMAL CLINICAL STAGING

Pre-treatment evaluation, including accurate staging, is critical when planning treatment for rectal cancer patients. The mainstay of treatment is surgery, which runs the gamut from local excision to radical resection with or without chemoradiation. Accurate staging is the first crucial, necessary step in optimizing therapy, maintaining quality of life, and limiting over- and under-treatment.

Most rectal cancers are diagnosed at colonoscopy, usually after patients present with asymptomatic anemia or change in bowel habits. Histologic confirmation is important, as benign stricture and inflammatory conditions may mimic malignancy. Full colonoscopy is necessary in order to identify synchronous polyps and malignancies, which occur in about 30% and 3%-5% of cases, respectively[4,5]. If the colon cannot be fully evaluated preoperatively due to colonic obstruction, it is recommended at 3-6 mo postresection[6].

Once a patient is diagnosed with rectal cancer, the most commonly ordered imaging study is computed tomography (CT). When properly performed with oral and intravenous contrast, CT provides important information regarding extent of disease. Although it is not a very accurate imaging modality for determining the degree of primary tumor penetration into the rectal wall or involvement of locoregional lymph nodes, CT scanning of the chest, abdomen and pelvis accurately identifies distant metastatic disease in the lung, liver, pelvic and periaortic lymph nodes.

Staging of the primary rectal lesion begins with a detailed digital rectal examination (DRE). This confers important information about the primary lesion, including its location with respect to the top of the anorectal ring (external sphincter complex) as well as its mobility. The degree of tumor fixity in the pelvis corresponds to depth of penetration through the rectal wall. Mobile lesions are often limited to the mucosa, submucosa or muscularis propria, whereas tethered lesions are likely to extend into the perirectal fat (mesorectum). A fixed lesion may signify extension of tumor into surrounding anatomic structures such as the seminal vesicles, prostate or vagina (T4 lesions). Rigid proctosigmoidoscopy provides the best estimate of tumor distance from the anal verge.

Endorectal ultrasonography (ERUS) and magnetic resonance imaging (MRI) are the most accurate tools for assessing T and N stage. ERUS is advantageous in imaging small, superficial tumors, whereas MRI is useful in evaluating bulky tumors that extend to the circumferential margin (CRM)[7]. Based on the results of large meta-analyses, the accuracy of ERUS in determining T and N stage is 87% and 74%, respectively[8]. The accuracy of MRI in determining T and N stage is 71%-91% and 45%-79%, respectively[9], similar to that of ERUS. Introduction of endoluminal coil MRI improves imaging resolution of the rectal wall. However, the true strength of MRI lies in phased-array MRI, which facilitates accurate assessment of tumor encroachment of the CRM, or invasion into surrounding anatomic structures[10]. Both MRI and ERUS are less accurate in assessing locoregional lymph node metastasis. Morphology, such as irregular border or heterogeneous intensity, is often more predictive than lymph node size[11]. It is important to remember that 18% of nodal metastases occur in lymph nodes measuring less than 5 mm[12]. Rather than being competing modalities, however, ERUS and MRI are often complimentary in the process of rectal cancer staging. ERUS is particularly useful in the staging of early rectal cancers; it also has the advantage of low cost, and can be performed quickly in the outpatient office. Phased-array MRI is much more expensive and not as readily available; however, it affords a comparatively greater field of vision, enhancing the ability to identify at-risk CRM and invasion of adjacent organs.

CHEMORADIATION: POSTOPERATIVE *VS* PREOPERATIVE

A paradigm shift in preoperative radiotherapy (RT) was introduced by the Swedish Rectal Cancer Trial in 1997. This study randomized 1168 patients to receive either one week of RT followed by surgery, or surgery alone. Compared with surgery alone, patients who received preoperative RT had reduced local recurrence (11% *vs* 27%, $P < 0.001$) and prolonged survival [5-year overall survival (OS) of 58% *vs* 48%, $P = 0.004$][13]. At a median follow-up of 13 years, the benefits in terms of local recurrence (9% *vs* 26%, $P < 0.001$) and OS (38% *vs* 30%, $P = 0.008$) remained significant in patients who received preoperative RT[14]; however, these patients did experience more gastrointestinal complications and had a higher rate of hospitalization over the 6-mo period following surgery[15].

Total mesorectal excision (TME) involves sharp dis-

section along the embryonic planes between the visceral and parietal layers of the endopelvic fascia. This ensures complete removal of locoregional lymph nodes contained within the mesorectum, while preserving the autonomic nerves and limiting blood loss. Multiple retrospective and cohort studies have shown that TME is associated with lower rates of local recurrence compared to the less optimal blunt surgical technique. The Dutch TME trial (published in 2003) was the first to compare the results of TME with and without preoperative short-course RT. Of 1861 accrued patients, 924 and 937 were randomized to receive either preoperative radiation followed by TME, or TME alone. Local recurrence was significantly lower in patients, who received preoperative RT plus TME (2.4% *vs* 8.2%, $P < 0.001$), but there was no difference in OS[16]. Long-term follow-up showed lower recurrence rates in the preoperative RT arm, especially in the subgroups of patients with nodal involvement, patients with tumor located between 5-10 cm from the anal verge, and patients with free CRMs[17].

While preoperative short-course radiotherapy consisting of 25 Gy in 5 fractions has been the favored treatment in Northern Europe and Scandinavia, in North America and in some European countries long-course chemotherapy has been the treatment of choice, based in part on the results of the Gastrointestinal Tumor Study Group and National Surgical Adjuvant Breast and Bowel Project (NSABP) trials. With theoretical advantages of better tolerance and increased efficacy, many centers moved toward preoperative neoadjuvant chemoradiation: 50.4 Gy delivered in 28 fractions, and concurrent fluoropyrimidine-based chemotherapy. The majority of patients receiving chemoradiotherapy obtain tumor downstaging (in which the final pathologic stage at time of surgery is lower than the initial clinical stage at time of presentation)[18]. Indeed, as many as 15%-20% of patients will have a complete pathologic response to treatment, with no viable tumor cells noted in the resected rectum. Tumor downsizing may facilitate complete tumor resection and, in the setting of low-lying tumors, may alter the surgical plan by making a sphincter-saving procedure possible[19,20].

Although two prospective, randomized controlled trials comparing preoperative and postoperative chemoradiation failed to accrue; NSABP R03[21] and the Intergroup 1047 trial[22] in the United States, the German Rectal Cancer Study Group successfully completed such a trial. The German CAO/ARO/AIO 94 trial[19] compared preoperative and postoperative long-course chemoradiation for T3 or T4 and/or node-positive rectal cancer. Chemoradiotherapy consisted of 50.4 Gy in 28 fractions with concurrent infusional fluorouracil (1000 mg/m^2 per day for 5 d in the first and fifth week of radiation). Four hundred twenty-one and 402 patients were randomly allocated to receive preoperative and postoperative chemoradiotherapy, respectively. There was 6% local recurrence in the preoperative group and 13% in the postoperative group ($P = 0.006$). Grade 3 or higher acute and long-term toxicity occurred significantly less frequently in patients who received neoadjuvant chemoradiation ($P = 0.001$ and $P = 0.01$, respectively). However, the rates of sphincter preservation, DFS and OS did not differ between the two groups.

Comparison of long- and short-course radiotherapy was the aim of a Polish randomized study[23,24] of patients with T3/4 mid to low rectal cancer. The results demonstrated higher rates of complete pathologic response in the group of patients receiving long-course chemoradiotherapy: 16% and 1% had complete pathologic response in the long-course and short-course chemoradiotherapy groups, respectively. Although rates of sphincter preservation were similar in both study groups, patients receiving long-course chemoradiotherapy had a 4% rate of positive CRM at time of surgery, compared with 13% in the short-course group ($P = 0.017$). However, there was no significant difference in local recurrence, DFS or OS.

The recently reported MRC CR07 and NCIC-CTG C016 multi-center randomized study[25] of 1350 patients compared the outcomes of preoperative short-course RT *vs* initial surgery followed by selective postoperative chemoradiation in patients with positive CRM. The primary outcome was local recurrence. This study demonstrated a significant decrease in local recurrence in patients receiving preoperative short-course RT (hazard ratio 0.39, $P < 0.0001$), which was associated with a 6% absolute improvement in DFS at 3 years ($P = 0.03$). Again, these data demonstrate the superiority of preoperative chemoradiotherapy.

The above data indicate that both preoperative long-course and short-course radiotherapy followed by proper TME provide excellent local control. The advantages of long-course chemoradiotherapy include tumor downsizing and downstaging, which may alter the surgical treatment plan in favor of a sphincter-preserving procedure. Long-course chemoradiation is associated with higher acute toxicity than short-course (18.2% *vs* 3.2%, respectively)[23]. On the other hand, short-course RT may lead to more long-term complications secondary to higher dose per fraction. In the United States, long-course chemoradiotherapy consisting of 5040 cGy, delivered concurrently with 5-fluorouracil (5FU) chemotherapy, is the most common regimen[6].

With improvements in surgical technique, including TME, the utility of chemoradiation in early T3 lesions without at-risk CRM has been called into question. A study of 95 T3N0 rectal cancer patients undergoing TME demonstrated less than 10% local recurrence rate without adjuvant therapy[26]. A pooled analysis of 3791 patients from several randomized studies showed no difference, in terms of OS, in T3N0 rectal cancer patients who received surgery plus chemotherapy with, or without, radiation (85% *vs* 74%-80%, respectively). Moreover, local relapse was similar among stage Ⅱ patients undergoing surgery alone (14%) or surgery plus radiotherapy (12%)[27]. It has been suggested that patients at lower

risk of local recurrence, e.g., those with proximal T3N0 lesions with clear margin, may be adequately treated by surgery and only adjuvant chemotherapy. However, correctly assessing T and N stage remains problematic. Two studies have reported the limitations of ERUS or MRI in determining accurate nodal stage, with false negative rates of up to 22%-28%[28,29]. Therefore, preoperative chemoradiation for clinical T3N0 rectal cancer patients should be considered by weighing the risk of unnecessary treatment against the possibility that the patient may ultimately require postoperative chemoradiation, which is associated with lower local control and higher toxicity than preoperative chemoradiation. Currently, preoperative chemotherapy remains the standard of treatment for T3N0 patients based on the principle that overtreatment is less harmful than undertreatment.

MAXIMIZING RESPONSE TO NEOADJUVANT CHEMORADIATION

Fluoropyrimidine-based chemotherapy synergizes with long-course radiotherapy. A 2 × 2 study of the European Organization for Research and Treatment of Cancer (EORTC) 22921 trial[30] assessed the efficacy of adding chemotherapy to RT, with or without adjuvant (postoperative) chemotherapy. The addition of chemotherapy at some point in the treatment regimen, either preoperatively or postoperatively, conferred a significant benefit in terms of local control. RT is fundamental to neoadjuvant treatment of rectal cancer, resulting in increased pathological response rate and better local control. However, it has no effect on distant metastasis. These findings imply that fluorouracil acts as a potent radiation sensitizer but has no significant eradicating impact on micrometastatic disease. In an attempt to improve response rates and reduce distant metastasis, new preoperative strategies are being investigated; these include combinations of new chemotherapeutic agents used concurrently with RT as well as induction chemotherapy. Currently efforts are being made to integrate novel agents in combination with RT, using the pathologic complete response (pCR) rate as a surrogate endpoint. Pathological CR has demonstrated correlation with clinical outcomes, i.e., relapse-free survival, DFS and OS[31,32].

Capecitabine, an oral pro-drug of fluoropyrimidine designed to enable selective 5FU activation in tumor tissue, has been studied as an agent used concurrently with RT. Several phase Ⅰ / Ⅱ studies have revealed a pCR rate of 7%-31% with acceptable toxicities[33-36]. Two randomized controlled trials showed capecitabine to be non-inferior to 5FU in the perioperative treatment of stage Ⅱ-Ⅲ rectal cancer. The NSABP R-04[37] compared the efficacy of continuous infusion 5FU to capecitabine delivered concurrently with preoperative RT, with or without oxaliplatin, in 1608 patients. The rates of pCR were 19% and 22% in patients who received 5FU and capecitabine, respectively (P = 0.12). Long-term outcomes of DFS and OS are awaited. Another phase Ⅲ trial from Germany[38] demonstrated that capecitabine, used in the neoadjuvant or adjuvant setting, is not inferior to 5FU in terms of 5-year OS (capecitabine 76%; 5FU 67%, P = 0.053). The use of oral capecitabine (825 mg/m^2 taken twice daily) throughout the course of radiation has been an alternative option; it is not inferior to infusional fluoropyrimidine in terms of efficacy or toxicity, and has the potential advantage of convenience for the patient.

The results of two phase Ⅲ studies studying combined oxaliplatin and fluoropyrimidine used concurrently with radiotherapy have also been reported. The ACCORD12 trial compared CRT using capecitabine + 45 Gy RT to capecitabine + oxaliplatin (CAPEOX) + 50 Gy RT[39]. This study showed pCR rates of 13.8% and 18.8% in the capecitabine/RT and CAPEOX/RT groups, respectively (P = 0.11). Another phase Ⅲ study from Italy investigated the efficacy of adding weekly oxaliplatin to protracted infusion of 5FU, concurrently with radiation, in locally advanced rectal cancer patients[40]. There was no difference in the pCR rate (16% in the 5FU group *vs* 15% in the 5FU + oxaliplatin group, P = 0.98). Interestingly, fewer patients in the 5FU + oxaliplatin arm were found to have metastatic disease after neoadjuvant chemoradiation (0.5% *vs* 3%, P = 0.014); this data may imply that oxaliplatin is potentially efficacious in controlling micrometastasis. Another trial of NSABP R-04[37], reported at the 2011 American Society of Clinical Oncology Annual Meeting, demonstrated that oxaliplatin does not improve pCR rates (19.1% *vs* 20.9%, P = 0.46), but significantly increases toxicity. However, neither randomized controlled trial showed any improvement in acute endpoints, i.e., pCR. At this time, single agent fluoropyrimidine, either infusional 5FU or capecitabine used concurrently with pelvic radiation, remains the standard of care in stage Ⅱ and Ⅲ rectal cancer.

Attempts have been made to integrate molecularly targeted therapy with preoperative combined modalities, in order to improve the efficacy of standard neoadjuvant chemoradiation. The addition of cetuximab to capecitabine was evaluated in a phase Ⅰ / Ⅱ trial in which only 5% of patients reached pCR; however, there was no unexpected toxicity[41]. Another study from Germany also reported a suboptimal pCR rate (9%) after preoperative cetuximab + capecitabine, oxaliplatin and radiotherapy[42]. Data on preoperative bevacizumab are limited to a few phase Ⅰ studies. However, in contemplating treatment with bevacizumab, the known adverse effects of this monoclonal antibody (such as bowel perforation, bleeding, and impaired surgical wound healing) must be considered.

Induction chemotherapy followed by neoadjuvant chemoradiation was considered a potential approach to controlling micrometastasis. A phase Ⅱ United Kingdom trial, using this new strategy of neoadjuvant chemotherapy with CAPEOX prior to CRT and surgery, has been reported[43]. One hundred five individuals, identified by high-resolution MRI as poor-risk rectal cancer patients, were enrolled. The definition of "poor-risk"

entailed one of the following features: CRM threatened or involved by tumor, low-lying tumor at or below the levators, T3 tumor with radial margin > 5 mm, T4 lesion, or N2 disease. The results showed the feasibility of this approach, with overall rates of 5-year and DFS 75% and 68%, respectively. In the setting of locally advanced rectal tumors, these are very impressive statistics.

A Spanish trial[44] was conducted to compare this new strategy with the more conventional approach of neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy. One hundred eight patients were randomized to receive 4 cycles of CAPEOX for the induction period, followed by neoadjuvant chemoradiation and then surgery; or else to receive neoadjuvant chemoradiation followed by surgery, and subsequently 4 cycles of adjuvant CAPEOX. There was no difference in pCR rate (13% *vs* 14%). Significantly less toxicity and a greater ability to tolerate chemotherapy throughout the schedule were found in patients who received induction chemotherapy. Another phase Ⅱ study from Memorial Sloan-Kettering Cancer Center[45] was conducted to determine the efficacy of induction chemotherapy, followed by chemoradiotherapy and then surgery, for stage Ⅲ or potentially resectable stage Ⅳ rectal cancer patients. Thirty-four patients were enrolled. Seventeen of 27 patients who ultimately underwent TME had > 90% pathological tumor response. At a median follow-up of 25 mo, no local recurrence was identified. Three-year DFS and OS were 63% and 100%, respectively, in patients with resected stage Ⅲ rectal cancer. This study showed a promising clinical outcome with tolerable toxicity. We believe that this approach will become one of the mainstays of treatment for patients with locally advanced rectal cancer in the future, but the data must be borne out in larger phase Ⅲ studies.

PREDICTORS OF RESPONSE TO NEOADJUVANT THERAPY

Several parameters associated with tumor response to neoadjuvant chemoradiation have been identified. Some studies have concluded that lower pre-treatment carcinoembryonic antigen (CEA) level is associated with better response to treatment[46-50]. The cut-off CEA levels associated with response rate were 2.5[46], 3[47], and 5 ng/mL[48-50]. However, because the pre-treatment CEA level in a majority of patients is normal and the cut-off level inconclusive, the applicability of CEA in predicting treatment response remains unclear.

Location of tumor, including tumor distance from the anal verge and the extent of luminal involvement by tumor, has also been examined. Bulky T3 lesions are less likely to show significant downstaging[51]. In a study of 247 patients, T3 tumors with > 2.5 mm extension into the mesorectum demonstrated a lesser response to therapy, with a low degree of downstaging[51]. It cannot be determined if this is merely attributable to tumor volume or to actual tumor biology. Predictably, this study also noted that poorly differentiated histology and metastatic disease were associated with limited response to treatment. Similarly, other reports have found that there is comparatively less downsizing in lesions with > 60% circumferential involvement. Interestingly, in this study lesions located higher than 5 cm from the anal verge were more likely to show a significant response to neoadjuvant chemoradiation[46].

In the past decade, many studies have attempted to identify correlations between immunohistochemical biomarkers such as Ki-67, p53, p21, bax/bcl2, epidermal growth factor receptor, thymidylate synthase, and tumor response after neoadjuvant chemoradiation. Currently, however, these studies remain inconclusive[52-54].

RESTAGING AFTER NEOADJUVANT CHEMORADIATION

Identifying the 15%-20% of patients who achieve a complete response to neoadjuvant therapy remains a challenge. Because of their fundamental roles in the neoadjuvant chemoradiation setting, DRE, endoscopy, ERUS, CT, MRI and positron emission tomography (PET) have been proposed as investigational tools to determine tumor response to treatment. The problem is that none of these modalities are capable of accurately predicting pCR[55], the reason being that fibrosis and inflammation caused by radiation have a deleterious affect on accuracy. A study from our institution[56] demonstrated that DRE is an inaccurate method for determining response to treatment after neoadjuvant chemoradiation; the overall concordance between DRE and pathologic response following neoadjuvant chemoradiotherapy was only 22%. A study from Italy showed that only half of patients who were defined as having complete response on endoscopic biopsy had true pCR according to pathology from surgical resection[55].

The accuracy of ERUS and MRI in the setting of post-neoadjuvant chemoradiation is also limited. A prospective study compared the accuracy of CT, MRI and ERUS *vs* pathologic assessment in determining clinical T and N stage in 90 patients receiving long-course neoadjuvant chemoradiation. The accuracy of these imaging modalities in determining T stage was low (37% by CT, 34% by MRI, and 27% by ERUS); most of this was due to over-staging. The rate of accuracy in nodal staging was 62% by CT, 68% by MRI and 65% by ERUS[57].

Because of the limited accuracy of all existing imaging modalities in staging rectal cancer post-neoadjuvant chemoradiation, several groups have investigated novel imaging methods. Diffusion-weighted MRI is a functional MRI imaging technique with better accuracy than that of conventional MRI[58-60]. However, the role of this emerging method is still investigational, and more studies with larger numbers of patients are awaited. In the meantime, repeat CT of the chest, abdomen and pelvis is useful in identifying development of interval metastatic disease, the presence of which could alter the surgical plan.

PET is a functional imaging study. Theoretically, the change of activity in the tumor should relate to the treatment response. Support to this idea, there are some studies demonstrated the relative change of maximum standardized uptake value relate to tumor response[61-63]. On the contrary, the data from another study demonstrated 63% sensitivity and 74.4% specificity of PET to predict patients with complete response[64]. While, PET is sometimes utilized in the process of restaging, the current data on the efficacy of this modality is inconsistent and limited; thus we do not routinely use PET as a restaging tool.

OPTIMAL TIMING OF SURGERY AFTER NEOADJUVANT THERAPY

In an attempt to increase response to chemoradiation, some groups have investigated lengthening the interval between chemoradiotherapy and surgery. Traditionally, surgery has been recommended 6-8 wk after neoadjuvant chemoradiation[65-69] to allow for tumor regression without extensive fibrosis. Indeed, several studies have shown that extending the period between chemoradiation and surgery may increase rates of complete pathologic response without increasing perioperative complications[63-65]. However, the effect of a longer interval on long-term outcome has yet to be defined. A well-designed multicenter prospective trial of increasing the interval between neoadjuvant chemoradiation and surgery is ongoing[70]. It is unclear if this will impact outcome; nevertheless, it may be of significance in the development of nonoperative strategies (see below). Some have also proposed adding chemotherapy to the waiting period, in an attempt to treat potential micrometastatic disease[71,72]. Habr-Gama *et al*[71] have reported the preliminary results of a study adding chemotherapy in the interval between neoadjuvant chemoradiation and surgery, which demonstrate an increased rate of complete clinical response.

MINIMALLY INVASIVE SURGERY FOR LOCALLY ADVANCED RECTAL CANCER

Laparoscopic surgery for rectal cancer has been proven feasible, but it is not yet a standard treatment in the United States. The United Kingdom Medical Research Council Trial of Conventional *vs* Laparoscopic-Assisted Surgery in Colorectal Cancer trial[73] demonstrated equivalent long-term recurrence and survival results in rectal cancer patients who did not receive neoadjuvant treatment. The Comparison of Open *vs* Laparoscopic surgery for Mid and Low Rectal Cancer after Neoadjuvant Chemoradiotherapy trial[74] is a prospective randomized trial that includes 340 patients with locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy, randomized to laparoscopic and open groups in a ratio of 1:1. The conversion rate is only 1.2% (2 in 170 patients). From the short-term results, operative time is significantly longer in the laparoscopic group, but estimated blood loss was significantly less. The rate of positive circumferential resection margin did not differ significantly between the two groups; nor did distal resection margin. The long-term oncological outcomes are awaited.

PREDICTORS OF RECURRENCE AND SURVIVAL

Several factors are reportedly predictive of recurrence and survival. Some of these features are the same in patients who receive or do not receive neoadjuvant chemoradiation. Some differ.

Post neoadjuvant chemoradiation CEA level

It has been proposed that post-neoadjuvant chemoradiation CEA levels < 2.5 ng/mL[75] and 5 ng/mL[76] are associated with significantly better DFS and OS. Another study, however, discerned no correlation[77]. Moreover, most studies focusing on correlations between predictors and long-term outcomes do not focus on CEA levels[77-79]. Thus, application of this parameter in attempting to predict recurrence and survival remains inconclusive.

Tumor response and nodal status after neoadjuvant chemoradiation

The pathologic response of tumor to treatment is one of the most significant prognostic factors in rectal cancer[18,80]. In terms of recurrence and survival, pCR is most strongly correlated with excellent outcome[80-85]. Several tumor regression grading systems classify tumor response following neoadjuvant chemoradiation in patients with pathologic partial response. All of these grading systems are consistent and demonstrate a strong association between pathologic response and outcome[18,32,79,83]. In the setting of neoadjuvant chemoradiation, preoperative treatment reduces lymph node yield at the time of surgery. However, the ratio of positive lymph nodes to total lymph nodes is prognostic, and may in fact be a more useful prognostic factor than total number of lymph nodes culled following neoadjuvant chemoradiation[83]. Several studies have associated positive pathological lymph node (ypN) status with poor prognosis[30,77-83].

Distal resection margin

Historically, the standard guidelines have recommended a distal resection margin (DRM) of 4-5 cm from the distal edge of tumor[6,86]. However, several reports have found that a DRM < 2 cm does not increase recurrence rates[87,88] or negatively impact survival[88]. In the setting of low rectal cancer located < 5 cm from the anal verge, 1-2 cm may be acceptable[6]. Especially following preoperative treatment with neoadjuvant chemoradiation, the 1-2 cm DRM rule seems to be less important than obtaining a clear resection margin[89,90].

CRM

The standard cut-off point of the CRM is still a matter of controversy. Most published studies have used < or = 1 mm[91-93], 2 mm[94-96], or 5 mm[7,97] as acceptable cut-off points in chemoradiotherapy-naïve patients. All reported significantly higher recurrence rates and shorter survival in patients with CRM < or = 1 mm[91-93], 2 mm[94-96], or 5 mm, respectively[7,98]. Therefore, in patients who have not received neoadjuvant chemoradiation and whose pathology indicates a close CRM (less than 1-5 mm), adjuvant chemoradiation should be strongly considered regardless of other pathological results[90,98]. In patients who have already received neoadjuvant chemoradiation, adjuvant chemotherapy should be considered[95-97].

Perineural invasion and lymphovascular invasion

These are poor prognostic factors in colon and rectal cancer in general. Even with neoadjuvant chemoradiotherapy, Perineural invasion and lymphovascular invasion remain predictors of poor outcome[20,97].

Acellular mucin pools

Acellular mucin pools (AMP) has been found in 11%-27% of surgical cases after neoadjuvant chemoradiation[99,100]. The question is whether AMP after neoadjuvant chemoradiation should be considered residual disease or not. Several reports have concluded that AMP does not have a significant impact on outcome[99-101]. The College of American Pathologists has recommended that AMP not be interpreted as residual disease[102].

POSTOPERATIVE ADJUVANT CHEMOTHERAPY: IS IT NECESSARY?

There is a high risk of local recurrence and distant metastasis in stage Ⅱ and Ⅲ rectal cancer patients treated by surgery alone. The role of adjuvant chemotherapy is to eradicate micrometastatic disease. Patients with T3 or node-positive disease who are initially treated by transabdominal resection should receive six months of adjuvant therapy, consisting of a "sandwich regimen" of two-month fluoropyrimidine-based chemotherapy followed by concurrent chemotherapy and radiation, followed by another 2 mo of chemotherapy.

Previously, the standard adjuvant chemotherapy regimen for rectal cancer was 5FU with or without leucovorin. The use of combination oxaliplatin, 5FU and leucovorin (FOLFOX4) or capecitabine in adjuvant treatment has been extrapolated from data available for colon cancer. According to the MOSAIC trial[103], FOLFOX4 compared to 5FU + leucovorin improved DFS and OS in stage Ⅲ colon cancer patients. The X-ACT study[104] showed that, in terms of DFS and OS, the efficacy of capecitabine in adjuvant treatment of stage Ⅲ colon cancer was comparable to that of 5FU + leucovorin.

There has been much consideration of the need for adjuvant chemotherapy in patients who have already received preoperative chemoradiation. The EORTC 22921 study[28,105] assessed the value of adjuvant chemotherapy in patients undergoing preoperative CRT followed by surgery. Patients were allocated into four arms: preoperative RT; preoperative CRT; preoperative RT + adjuvant chemotherapy; and preoperative CRT + adjuvant chemotherapy. No difference in OS was found between the groups receiving preoperative and postoperative chemotherapy (P = 0.12). The addition of chemotherapy after preoperative CRT did not impact rates of local recurrence or survival. Of concern, however, is the fact that only 42.9% of assigned patients adhered to their postoperative chemotherapy regimens. DFS and OS benefits were shown in the subgroup of patients with pathological T (ypT) 0-2 cancers[106]. These results indicate that patients who do obtain downstaging after CRT may be more likely to derive a survival benefit from adjuvant chemotherapy as well.

Given that most of the patients in EORTC 22921 did not receive adequate doses of adjuvant chemotherapy, we cannot assume from this study that adjuvant chemotherapy is definitely not beneficial to patients receiving neoadjuvant chemoradiation. To date, preoperative chemoradiation followed by surgery and adjuvant chemotherapy remains the standard of practice in the United States for treating stage Ⅱ and Ⅲ rectal cancers[6] regardless of final pathological results. Options for adjuvant chemotherapy include four months of FOLFOX, capecitabine, or 5FU + leucovorin.

CLINICAL COMPLETE RESPONSE: CAN SURGERY BE AVOIDED?

Habr-Gama *et al*[107] have proposed a definition of clinical complete response (cCR), based on the findings of clinical and endoscopic examination, as follows: (1) whitening of the mucosa in an area of the rectal wall; (2) any associated telangiectasia; (3) scarring of the rectal wall (which manifests as a slight stiffness of the wall during insufflation); and (4) if tumor cannot be felt or seen. These parameters are subjective, however, and require more clinical substantiation. Moreover, cCR may not be equivalent to pCR. Surgery is still the standard of management following neoadjuvant chemoradiation[6,86].

There have been studies of local excision as an option for patients with cCR after neoadjuvant chemoradiation[108,109]. However, complete response of the primary tumor cannot predict response in regional lymph nodes, which are involved in 7%-17% of patients who have cCR of the primary tumor[110-112]. For this reason local excision may not be adequate treatment of these patients. In the setting of low-lying rectal cancer, sphincter-preserving procedures (intersphincteric dissection with coloanal anastomosis) may be performed in patients who obtain a tremendous response from neoadjuvant chemoradiation[20].

Habr-Gama *et al*[113] have also reported very interesting long-term outcomes of observational management in patients with cCR following neoadjuvant chemoradiation. They selected the 122 of 361 patients who received

neoadjuvant chemoradiation and were considered to have cCR. These patients had very low rates of both local recurrence and distant metastasis (5% and 7%, respectively). Isolated local recurrences confined to the rectum developed in 5% of patients over a median follow-up period of 59.9 mo[114]. Significantly more data from larger studies will be required to evaluate this approach. Nevertheless, observational management may be an alternative choice for some carefully selected patients.

CONCLUSION

Concurrent chemoradiotherapy is widely accepted as an effective way to achieve local control and survival in patients with locally advanced rectal cancer. The accuracy of preoperative staging is crucial in preventing under- or over-treatment. ERUS and MRI are suitable imaging tools for local preoperative staging, while CT and PET are helpful in evaluation of metastasis. Fluoropyrimidine-based chemotherapy (either 5FU or capecitabine) used concurrently with radiotherapy is the standard treatment. The addition of oxaliplatin increases toxicity without having any significant impact on tumor sterilization.

Optimal timing of surgery remains unclear. Previous recommendations to resect at 6-8 wk after neoadjuvant chemoradiation appear reasonable; but a longer interval may increase tumor downsizing. However, the effect of a longer waiting time on long-term outcome is yet to be defined.

The accuracy of studies attempting to determine tumor response remains problematic. Clinical complete response, as determined by existing methods, may not be equivalent to pCR. At this time, surgery remains the standard of care for rectal cancer patients following neoadjuvant chemoradiation. Observational management is still investigational but may be used in carefully selected high-risk patients, ideally in the setting of a clinical trial. Pathologic features such as ypT, ypN, tumor response, and CRM are accurate prognostic factors associated with long-term outcome.

Extrapolating from colon cancer trials, adjuvant chemotherapy (5FU/leucovorin, capecitabine or FOLFOX) remains the standard of care following rectal cancer resection, irrespective of pathologic response. Future directions will require a rethinking of management strategies, and may include different optimal drug combinations, treatment sequences, and approaches to neoadjuvant radiation, chemotherapy and/or targeted therapy. The goal is to achieve improvement in response and patient survival. The challenges include individualizing care to improve long-term oncologic outcome, while minimizing toxicity and maintaining quality of life.

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