World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i8.2023

World J Gastroenterol 2014 February 28; 20(8): 2023-2029
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Current issues in locally advanced colorectal cancer treated by preoperative chemoradiotherapy

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Received: September 28, 2013 Revised: November 26, 2013
Accepted: January 6, 2014
Published online: February 28, 2014

Abstract

In patients with locally advanced rectal cancer, preoperative chemoradiotherapy has proven to significantly improve local control and cause lower treatment-related toxicity compared with postoperative adjuvant treatment. Preoperative chemoradiotherapy followed by total mesorectal excision or tumor specific mesorectal excision has evolved as the standard treatment for locally advanced rectal cancer. The paradigm shift from postoperative to preoperative therapy has raised a series of concerns however that have practical clinical implications. These include the method used to predict patients who will show good response, sphincter preservation, the application of conservative management such as local excision or "wait-and-watch" in patients obtaining a good response following preoperative chemoradiotherapy, and the role of adjuvant chemotherapy. This review addresses these current issues in patients with locally advanced rectal cancer treated by preoperative chemoradiotherapy.

Key words: Colorectal cancer; Rectal cancer; Preoperative chemoradiotherapy; Conservative; Response

Core tip: In the era of preoperative chemoradiotherapy for rectal cancer, issues such as treatment plan according to response which included application of organ preserving strategies, prediction of response, and role of adjuvant treatment were need to be discussed under circumstances that preoperative chemoradiotherpay spread widely as a standard treatment of rectal cancer.

Park IJ, Yu CS. Current issues in locally advanced colorectal cancer treated by preoperative chemoradiotherapy. *World J Gastroenterol* 2014; 20(8): 2023-2029 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i8/2023.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i8.2023

INTRODUCTION

Preoperative chemoradiotherapy (PCRT) has been used increasingly to treat locally advanced rectal cancer since it was proven to be beneficial in reducing the rate of local recurrence. A German trial[1] has reported that patients treated with PCRT had significantly lower local failure rates and toxicity rates than those receiving postoperative chemoradiotherapy (CRT), and PCRT was also found to produce a better outcome in terms of sphincter preservation. These findings led to a paradigm shift from postoperative to preoperative CRT so that PCRT has now become the standard treatment for cT3-4 and/or node-positive rectal cancer. This shift has however raised a series of concerns that have practical clinical implications such as a prediction of the responsiveness to PCRT, the application of conservative management such as local excision in patients obtaining a good response to this intervention, sphincter preservation, and the role of adjuvant chemotherapy. In this review, we discuss these issues.

Table 1 Local excision after preoperative chemoradiotherapy for rectal cancer *n* (%)

Ref	Year	*n*	inclusion	Complete remission	Local recurrence	Follow-up duration, mo	Overall survival
Kim *et al*[10]	2001	26	cT2-3 CR after PCRT	17 (65.4)	1 (3.8)	19	100%
Bonnen *et al*[11]	2004	26	cT3N0 or N1 CR after PCRT	14 (53.8)	2 (7.7)	46	5 yr OS; 85%
Huh *et al*[58]	2008	9	cT2-3N0 or N1	4 (44.4)	1 (11.1)	91	10 yr OS; 88.9%
Nair *et al*[59]	2008	44	cT2-3N0 or N1	19 (43.2)	4 (9.1)	64	5 yr OS; 84
Guerrieri *et al*[9]	2008	145	CR after PCRT cT2-3N0	17	8 (4)	81	100% (pT0-1) 90% (pT2) 77% (pT3)
Kundel *et al*[60]	2010	14	CR after PCRT	All	0	47	100%
Yu *et al*[17]	2013	40	cT2-3N0	19 (47.5)	4 (7.5)	38	3 yr DFS: 85.9%
Perez *et al*[61]	2013	27	cT2-3N0-2	3 (11.1)	4 (14.8)	15	1 yr DFS: 68%

CR: Complete remission; PCRT: Preoperative chemoradiotherapy (CRT); OS: Overall survival; DFS: Disese-free survival.

ORGAN PRESERVING STRATEGIES

Local excision

Although the standard management of locally advanced rectal cancer treated by PCRT is radical surgical resection, conservative management (local excision or close observation) has been used in some cases. The local excision of rectal cancer has been employed as surgical procedure for patients with early rectal tumors limited to the mucosa and submucosa. In early T1 tumors without high risk features, full thickness local excision alone has been shown to produce comparable long-term outcomes to radical surgery[2]. Complete regression of the tumor was reported to occur in up to 20% of patients with rectal cancer after PCRT[3-6]. Some investigators have performed local excisions to avoid possible morbidities such as permanent stoma formation and functional impairments in patients who showed a good response to PCRT, with many studies reporting that such cases subsequently had acceptably low rates of local recurrence and long-term survival outcomes comparable to radical surgery[7-11]. The promising results from these studies have encouraged interest in the possibility of avoiding radical surgery in some patients after PCRT and thus preserving sexual and urinary function, sparing rectal function, and, in cases of low rectal cancer, avoiding permanent stoma (Table 1).

However, the interpretation of the above data is confounded by the predominantly retrospective nature of the studies on rectal cancer to date. Moreover, these earlier studies cannot be directly compared due to the significant heterogeneity with respect to patient and tumor characteristics resulting from a lack of consistent staging and selection criteria. In addition, no mesorectal lymphadenectomies were undertaken for these previous study cohorts and the lymph node stages were undefined. More importantly, the extent and quality of the local surgery is likely to have significantly varied between studies, depending on the individual techniques used and the skills of the surgeons involved.

One of the great uncertainties when conducting local surgery is the status of the mesorectal lymph nodes. Some studies have confirmed that there can be differential responses between the primary tumor and the mesorectal lymph nodes[12,13]. The proportion of lymph node metastases reported in pathological complete response (pCR) cases is low, with a median rate of 7% ranging from 2% to 11%[12-14]. The potential caveat of using mural response as the only criterion for selecting patients for local excision was highlighted in a retrospective study of 242 patients following PCRT[15]. The incidence of lymph node involvement was 3.2% in patients developing mural pCR (ypT0) compared to 11% for ypT1 tumors and increased further as the ypT stage increased (ypT2 = 29.2%; ypT3 = 37.3%). When nodal involvement is understaged and patients undergo local excision, the prognosis is poorer. Recently, the American College of Surgeons Oncology Group has completed the Z6041 phase Ⅱ trial of patients with clinical T2N0 rectal cancer who received PCRT (total dose, 54 Gy) with capecitabine and oxaliplatin followed by transanal local excision 6 weeks after the completion of PCRT[16]. Of the 77 patients in that report who underwent local excision, 34 achieved a pCR (44%), 49 (64%) had ypT0-1, and 4 (5%) had ypT3 tumors. All but one patient had negative margins. Acute toxicity of at least grade 3 during PCRT occurred in 39% of these patients, and rectal pain was the most common postoperative complication. Colorectal Cancer Study Group in Korea also reported results of multicenter study for local resection after PCRT[17]. They reviewed 40 patients with cT2-3N0M0 treated with PCRT followed by local excision retrospectively. Among them, Four patients (7.5%) had recurrence [local recurrence (1 patient) and systemic metastasis (3 patients)]. The 3-year disease-free survival rate was 85.9%. Only pCR was a recurrence-related prognostic factor (P = 0.040). Based on these findings, a longer follow-up is clearly needed to assess the oncologic outcome. Moreover, local excisions need to be performed with great care for sub-group of patients and credible methods to measure the treatment response or remaining disease after PCRT are required.

"Wait and watch"

Possibly the other challenge for improving conservative

treatment regimens for rectal cancers is to try to preserve not only the anal sphincter but also the whole organ. Habr-Gama is proposing a strategy comprising PCRT and "watch and wait" in cases of a clinical complete response (cCR) with no radical surgery[18]. Data from a Brazilian series have demonstrated excellent long-term local control and OS rates in patients developing cCR after PCRT[18]. 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 a histologic complete response.

The ability to identify patients with a cCR who are also likely to have a pCR would have major clinical implications. If such information were available and accurate, it could obviate the need for radical surgery and possibly prevent a permanent stoma in selected patients. The limitations of clinical assessments after PCRT were demonstrated in a prospective series of 94 patients who underwent an assessment with digital rectal examination (DRE) and sigmoidoscopy both prior to and after the completion of PCRT[19]. These clinical assessments underestimated the pathologic response in 73 patients and DRE was able to identify only three of 14 cases (21%) with a pCR. The overall concordance between clinical evaluation and actual pathologic response was only 22%[19]. In another retrospective review of 488 patients with rectal cancer following PCRT, the cCR rate for the entire cohort was 19%, but only 10% had a true pCR[20]. Glynne-Jones *et al*[21] reviewed 218 phase Ⅰ / Ⅱ and 28 phase Ⅲ trials of preoperative radiotherapy or PCRT. 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.

It is not surprising therefore that the Brazilian experience has generated intense debate with some investigators expressing concerns about employing a policy of watchful expectancy based entirely on the presence of cCR after PCRT[22,23].

It is notable that other investigators have been unable to reproduce these aforementioned results. Hughes *et al*[22] reported a 60% intrapelvic recurrence rate in 10 cases with a cCR and concluded that a 'wait and see' policy could not be justified in T3 or 4 rectal cancers after PCRT. Nakagawa *et al*[24] also reported a high (80%) local recurrence rates and suggested that an exclusive PCRT approach is not safe for treating patients with low locally advanced rectal cancer. Such a strategy, however, could be of specific interest in elderly and vulnerable patients who are not fit for conventional surgery. It is possible that (full thickness) trans-anal local excision could be more relevant than observation alone after PCRT in such cases. Some phase Ⅱ and Ⅲ trials (ACOSOG Z 6041; GRECCAR 2; CONTEM 2) are currently ongoing to test this strategy.

PREDICTION OF TREATMENT RESPONSE

The response to PCRT differs among individual tumors and there currently is no effective method of predicting which patients will respond favorably to this treatment. Although positive responders to PCRT will experience the benefits of this intervention approach, patients who do not respond to PCRT will be exposed to unnecessary toxicities and surgery delay. It is therefore of the utmost importance to predict the treatment response and outcomes before initiating PCRT. Although a number of postsurgical prognostic factors have been proposed, patients with pCR after PCRT cannot at present be predicted by clinical examination or radiologic imaging procedures. The identification of basal resistance biomarkers could offer great help in this regard. Directed strategies that explore individual markers have not so far yielded clinically validated assays[25-27]. Past efforts to develop a predictive assay of tumor radio-sensitivity have been recently reviewed[28] and can be grouped into three categories: assays to determine intrinsic radiosensitivity (*ex vivo* determination of tumor survival fraction at 2 Gy)[29-32]; assays to determine tumor oxygen levels (electrodes to measure tumor pO2)[33,34]; and determination of tumor proliferative potential[35,36]. Unfortunately, although initial clinical data supported each of these approaches, none has become routine. A central reason for this has been that all of these approaches are highly impractical as a routine clinical application. The generation of high-throughput data sets has provided an opportunity to address the identification of biomarkers from a different perspective.

ADJUVANT CHEMOTHERAPY IN ADDITION TO PCRT AND SURGERY

There is no uniform agreement regarding the role of chemotherapy in addition to PCRT although current guidelines recommend additional adjuvant chemotherapy after PCRT regardless of the tumor response. Since most locally advanced rectal cancer patients have pathologically negative nodes following PCRT, some clinicians have argued that systemic therapy is not indicated. This argument is in part due to the lack of a proven survival benefit of chemotherapy in node negative colon cancer cases. The controversy is further illustrated by the fact that the European Organization for the Research and Treatment of Cancer (EORTC) is conducting a phase III trial in which patients are randomized to receive either 5-fluorouracil (5-FU) based chemotherapy or no further therapy following PCRT and radical resection.

The authors of the EORTC 22921 study reported that subgroups of patients achieving a pCR or who were downstaged to a ypT1-2 tumor category after preoperative radiation, benefited from adjuvant chemotherapy, whereas those with residual ypT3-4 disease did not[37]. These authors suggested the beneficial effects of adjuvant chemotherapy based on pathologic results, but they analyzed ypT and ypN categories separately. They also reported that adjuvant chemotherapy provided a benefit in patients who received a ypT downstage, but not in ypN0 or ypN-positive patients. Some data did not

confirm results of EORTC 22921 especially in terms of the effect of adjuvant chemotherapy on patients achieving pCR[38,39]. Chemotherapy is rarely indicated when the 5-year free-from recurrence rate exceeds 95%, which occurs in a complete pathological response. Considering the favorable outcome of patients with a complete response, survival outcomes with adjuvant chemotherapy is difficult to be improved than those of patients without adjuvant chemotherapy.

When evaluating subgroups of patients who may or may not benefit from adjuvant therapy after PCRT followed by resection, the benefit of adjuvant therapy for node-negative patients on final pathologic staging (ypN0) would be expected to be especially questionable. There is a paucity of information in the literature on whether adjuvant therapy improves survival for locally advanced rectal cancer patients with a stage ypN0 tumor. These findings are consistent with the suggestion by Fietkau *et al*[39] that postoperative chemotherapy may be unnecessary in ypN0 cases. Das *et al*[40] have insisted that postoperative chemotherapy may be of greater benefit for high-risk patients. However, their results are contrary to those of Janjan *et al*[41], who found a significant improvement in cancer-specific survival in response to PCRT and the addition of postoperative chemotherapy. In that study, it was suggested that patients who responded to 5-FU during PCRT would probably also respond to 5-FU-based postoperative chemotherapy.

Adjuvant chemotherapy for patients who do not show a good response to PCRT needs to be different from that administered to patients showing a good response to this treatment. Das *et al*[40] have recommended adjuvant FOLFOX for high-risk patients, and adjuvant FL or capecitabine for low-risk patients. This seems to be a reasonable approach to the postoperative adjuvant treatment of rectal cancer patients treated with PCRT. Until now, however, oxaliplatin has been the drug of focus in terms of outcome benefits as part of a preoperative multimodality treatment regimen[42-44]. The role of postoperative adjuvant chemotherapy following PCRT and radical resection for patients with locally advanced rectal cancer thus remains unclear.

SPHINCTER PRESERVATION

Avoiding permanent stoma is an important quality of life issue for rectal cancer patients[45]. An advantage of tumor shrinkage after PCRT is supposedly an increased chance of sphincter preservation[46,47]. However, this is a very complex issue involving the stage and location of the tumor, the patient habitus and desire, and the surgeon`s experience. Although an increase in the rate of sphincter preservation was reported in early PCRT trials, no such trials since 1980 have been able to demonstrate this. This may be due to the immediateness of the surgery after the end of a short-course of PCRT[48-51] which gives little opportunity for tumor shrinkage. However, despite an increased rate of pCR of up to 16%-19% in the latest PCRT trials[42,52], no benefit has been evident in terms of the sphincter preservation rate.

Two randomized trials[1,53] of preoperative and postoperative CRT for clinically resectable locally advanced rectal cancer have reported opposing results. In a German trial[1], of the 194 patients assessed by the surgeon before treatment as requiring APR, there was a significant improvement in sphincter preservation with preoperative therapy. However, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial[53], based on a prospective assessment by the operating surgeon, there was no reported improvement in sphincter preservation (PCRT: 47.8%; postoperative CRT = 39.2%; $P = 0.227$). The results of the NSABP R-03 trial, however, 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 potential benefits of this approach. In the recent Australian[54] trial where the two treatment arms were quite different (short course with immediate surgery *vs* chemoradiotherapy and delayed surgery) there was a reported increase in sphincter preservation of 8% in the delayed surgery arm. However, this was not significant because the number of patients assessed was too small. Weiser *et al*[55] reported a benefit of PCRT in terms of sphincter preservation from a retrospective analysis of 148 rectal cancer patients (within 6 cm of the anal verge).

The pooled data from 19 trials[56] favors PCRT, although not in a statistically significant way (0.94, 95%CI: 0.88-1.04) (Comparison 01:09). These data were borderline however in terms of homogeneity ($P = 0.05$), indicative of variations in the magnitude of effect across reports. In a recent review that analyzed the findings of 17 randomized trials the authors concluded that none of the neoadjuvant treatments tested could demonstrate an increase in the rate of sphincter-preserving surgery[57]. However, the effects of conservative treatments such as local excision or "wait-and-watch" on sphincter preservation were not considered in these analysis.

Until now, the evidence has been that an improved sphincter preservation benefit of PCRT was unclear. As described earlier, however, the link between PCRT and sphincter preservation needs to be evaluated with great care with consideration of tumor, patients and surgeon factors together. In addition, the effect of conservative management after PCRT need to be considered under condition the oncologic safety of this strategy is confirmed. The influence of PCRT on sphincter preservation needs to be re-evaluated under recent circumstances.

CONCLUSION

PCRT for locally advanced rectal cancer has been established as a standard treatment, but some issues regarding its practical application still need to be evaluated. In ad-

dition, an accurate prediction of the response to PCRT before administering this intervention, as well as an evaluation of nodal involvement after PCRT, remain important issues. An acceptable prediction of the response to PCRT should be integral to the decision making regarding an extension or selection of this treatment option.

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ISSN 1007-9327

9 771007 932045