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Contents

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ABOUT COVER

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AIM AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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ORIGINAL ARTICLE

Clinical Practice Study

Neoadjuvant hyperfractionated accelerated radiotherapy plus concomitant 5-fluorouracil infusion in locally advanced rectal cancer: A phase Ⅱ study

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Abstract

AIM

To evaluate the efficacy and tolerability of neoadjuvant hyperfractionated accelerated radiotherapy (HART)

and concurrent chemotherapy in patients with locally advanced infraperitoneal rectal cancer.

METHODS

A total of 30 patients with histopathologically confirmed T2-3/N0+ infraperitoneal adenocarcinoma of rectum cancer patients received preoperative 42 Gy/1.5 Gy/18 days/bid radiotherapy and continuous infusion of 5-fluorouracil (325 mg/m^2). All patients were operated 4-8 wk after neoadjuvant concomitant therapy.

RESULTS

In the early phase of treatment, 6 patients had grade Ⅲ-Ⅳ gastrointestinal toxicity, 2 patients had grade Ⅲ-Ⅳ hematologic toxicity, and 1 patient had grade Ⅴ toxicity due to postoperative sepsis during chemotherapy. Only 1 patient had radiotherapy-related late side effects, *i.e.*, grade Ⅳ tenesmus. Complete pathological response was achieved in 6 patients (21%), while near-complete pathological response was obtained in 9 (31%). After a median follow-up period of 60 mo, the local tumor control rate was 96.6%. In 13 patients, distant metastasis occurred. Disease-free survival rates at 2 and 5 years were 63.3% and 53%, and corresponding overall survival rates were 70% and 53.1%, respectively.

CONCLUSION

Although it has excellent local control and complete pathological response rates, neoadjuvant HART concurrent chemotherapy appears to not be a feasible treatment regimen in locally advanced rectal cancer, having high perioperative complication and intolerable side effects. Effects of reduced 5-fluorouracil dose or omission of chemotherapy with the aim of reducing toxicity may be examined in further studies.

Key words: Hyperfractionated accelerated radiotherapy; Rectal cancer; Neoadjuvant chemoradiotherapy

Core tip: This study includes a first phase Ⅱ study evaluating neoadjuvant hyperfractionated accelerated radiotherapy plus concomitant infusional 5-fluorouracil (5-FU) chemotherapy in locally advanced rectal cancer (not resectable cancer). This regimen may allow clinicians to design other neoadjuvant hyperfractionated accelerated radiotherapies. This study showed excellent local control but high rate of perioperative complications. Decreasing or modifying the 5-FU dose could provide better local control.

Gural Z, Saglam S, Yucel S, Kaytan-Saglam E, Asoglu O, Ordu C, Acun H, Sharifov R, Onder S, Kizir A, Oral EN. Neoadjuvant hyperfractionated accelerated radiotherapy plus concomitant 5-fluorouracil infusion in locally advanced rectal cancer: A phase Ⅱ study. *World J Gastrointest Oncol* 2018; 10(1): 40-47 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i1/40.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i1.40

INTRODUCTION

Rectal cancer is associated with a high incidence of local recurrence and distant metastasis[1,2]. In randomized studies, local-regional recurrence despite mesorectal resection has been reported to occur in 15% to 30% of the patients undergoing surgery alone[3-8]. In this regard, addition of preoperative and postoperative treatments to surgery have been shown to significantly improve local recurrence and survival rates[9-13], leading to standard administration of such treatments. Currently, preoperative chemoradiation (CRT) is the preferred treatment regimen in these patients, owing to low local recurrence rates and higher chance of sphincter-sparing surgery; although, studies comparing preoperative and postoperative CRT are relatively limited.

Besides conventional radiotherapy (RT) consisting of 45-50 Gy/1.8-2 Gy/5-6 wk, hypofractionated and hyperfractionated accelerated RT (HART; 42 Gy/1.5 Gy/18 d) are also used. HART reduces the risk of repopulation in tumor cells by shortening the treatment time and increases the repair capacity of normal tissues after sublethal damage through the reduction of the fraction dose. Thus, a survival advantage is provided in favor of normal cells, since tumor cells exhibit a poor repair mechanism[14]. In this background, a fractionated HART scheme was examined in this study.

Therefore, this study was carried out to observe the early and late effects of HART regimen in combination with neoadjuvant chemotherapy in patients diagnosed with locally advanced rectal cancer.

MATERIALS AND METHODS

Patient selection

Previously untreated patients with histologically confirmed adenocarcinoma of the rectum (mid and distal ⩽ 12 cm from the anal verge) were included in the study at Istanbul University Oncology Institute. Patient inclusion criteria were as follows: presence of resectable tumor; Karnofksy performance score ⩾ 80; adequate bone marrow reserve (hemoglobin > 11 g/dL, white blood cell > 3500 mL, platelet count > 100000 mL), normal kidney and liver function tests (creatinine < 1.3 mg/dL, alanine aminotransferase and aspartate aminotransferase < 80 U/L), and ⩽ 70 years of age. Patients who had received pelvic RT previously and patients with clinically detected distant metastases were excluded from the study. Clinical staging prior to treatment was accomplished based on physical examination, tumor markers (carcinoembryonic antigen, CA19-9), complete blood count and biochemistry tests, positron emission-computed tomography, pelvic-diffusion magnetic resonance imaging (MRI), and endorectal ultrasound. This prospective study was approved by the local ethics committee. A written informed consent was obtained from all patients prior to treatment.

Table 1 Patient characteristics

Characteristic	*n* = 30
Sex, M/F	19/11
Age, median (range)	53 (30-70)
Tumor location, distance from anal verge	
≤ 5 cm	19 (63)
> 5 cm	11 (37)
Clinical TN stage	
T2N2	1 (3)
T3N0	2 (7)
T3N1	15 (50)
T3N2	12 (40)
Tumor differentiation	
Well	10 (33)
Moderate	10 (33)
Poor	4 (14)
Mucinous	3 (10)
Signet ring cell	3 (10)

Unless otherwise stated, data are presented as *n* (%). M: Male; F: Female.

Preoperative CRT

All patients received preoperative HART (42 Gy/1.5 Gy/18 d/bid) and concurrent continuous infusion of 5-fluorouracil (5-FU; 325 mg/m^2) and were hospitalized during treatments to observe the possible acute side effects.

Prior to RT planning, computed tomography was performed in prone position with belly board, with a 0.5 cm slice thickness for all patients. Gross tumor volume and clinical target volume were estimated by the radiologist and radiation oncologist. Patients were treated with a 3-D conformal RT technique, through posterior and lateral fields using a linear accelerator (18 MV) and with an isodose of 95% of planned target volume. RT regimen was defined by a fraction dose of 150 cGy/fr given 2 times/d, 5 d/wk, with a minimum 8 h between fractions. Total dose was 4200 cGy and total treatment duration was 18 d.

Port or subclavian catheter was used to give 5-FU in the form of a continuous infusion during the entire treatment. The daily dose of 5-FU that was given to patients was 325 mg/m^2[15]. Surgery was performed 4-8 wk after the completion of CRT.

Low anterior or abdominoperineal resection (total mesorectal excision) was performed depending on the location of the tumor and response rate. Four cycles of 5-FU (400 mg/m^2, D1-5, q 28 d) plus folinic acid (20 mg/m^2, D1-5, q 28 d) were administered postoperatively.

Assessment of efficacy and side effects

The primary endpoint was pathological response rate after CRT, and secondary endpoints included the local control rate, surgical margin positivity, survival and toxicity. Patients were assessed for toxicity during CRT on a daily basis. During the period between the end of CRT and surgery, patient assessments for side effects were performed weekly. Acute radiation toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (EORTC) were used for side effect assessments[16]. Pathologic response and staging were defined according to the Dworak regression scoring system[17] and TNM staging system[18], as described by the American Joint Committee on Cancer.

Statistical analysis

Statistical analyses were performed with SPSS 16.0 (SPSS Inc., Chicago, IL, United States) statistical software. Survival was calculated using the Kaplan-Meier method.

RESULTS

Thirty patients (19 males and 11 females) who were diagnosed with locally advanced rectum cancer between October 2007 and March 2009 were included. The median age was 53 years (range: 30-70 years). Patient characteristics are summarized in Table 1. There were only 2 patients with T3N0 disease, and one of them had positive circumferential margins in staging MRI.

Pathological findings

Surgery was performed in all subjects except for one, who was found to have metastases during the early period after the CRT. Surgery was performed at week 4 in 15 patients and between weeks 6 and 8 in 13 patients. Twelve patients (41%) underwent sphincter-sparing surgery. According to the Dworak total regression scoring system, 6 of 29 (21%) patients who underwent surgery had grade Ⅳ (total) regression, and 9 patients (31%) had grade Ⅲ (near total) regression. Corresponding figures for grade Ⅱ, Ⅰ and 0 regression were 11 patients (38%), 2 patients (7%) and 1 patient (3%), respectively.

Positive margins were found in 2 patients (6.6%). In 14 patients, mesorectal fascia invasion was detected in staging MRI and only 2 of those patients had positive radial surgical margin. Comparison of ypT and cT yielded a down-staging rate of 59%. Clinical and pathological tumor stages are shown in Table 2. The median number of lymph nodes that were excised was 25 (2-58), respectively. No pathologic lymph nodes were present in 19 (63%) patients. With regard to N stage, 20 (69%) patients were found to have down-staging.

Local control and survival

One (3.3%) patient had local recurrence while distant metastases were found in 13 (43.3%) patients during a median follow up of 60 mo (5-78 mo). None of the patients with T3N0 disease had local recurrence. Overall, 14 patients (46.6%) died during the study period. The causes of death were systemic metastasis (13 patients) and chemotherapy-related toxicity (1 patient). Median time to progression was 59 mo (2-78

Table 2 Clinical (cT2) and pathological (ypT) tumor stages

	cT2	cT3	Total
ypT0	-	6 (20.6)	6 (20.6)
ypT1	-	3 (10.3)	3 (10.3)
ypT2	-	8 (27.5)	6 (20.6)
ypT3	1	11 (37.9)	12 (41.3)
Total	1	28	29

Data are presented as *n* (%).

Table 3 Surgical complications

Timing of the complication	
Perioperative	6 (20.6)[1]
Early postoperative	4 (13.7)[2]
Late postoperative	2 (6.8)[3]

[1]Bladder-urethra injury (*n* = 4), rectum perforation (*n* = 1), necrosis due to proctotectomy (*n* = 1); [2]Acute renal failure (*n* = 3), perirectal abscess (*n* = 1); [3]Colovaginal fistula (*n* = 1), perirectal abscess (*n* = 1). Data are presented as *n* (%).

mo). The 2- and 5-year disease-free survival (DFS) rates were 63% and 53%, while the 2- and 5-year overall survival (OS) rates were 70% and 53.1%, respectively. The patients with complete or near-complete pathological response were compared to patients with less favorable group for survival. We found no significant difference in either group for DFS (P = 0.63) and OS (P = 0.32).

Toxicity and complications

Early side effects of preoperative CRT: The highest frequency of side effects occurred at weeks 3-4. During the acute phase 6 (20%) patients developed grade Ⅲ-Ⅳ gastrointestinal system toxicity (3 grade Ⅲ tenesmus/diarrhea and 3 grade Ⅳ tenesmus and diarrhea), and 2 (6.7%) patients developed grade Ⅲ-Ⅳ hematopoietic system toxicity (1 grade Ⅲ leucopenia and 1 grade Ⅳ neutropenia). There were no interruptions in RT due to toxicity, while in 4 patients chemotherapy was interrupted for 1 wk. Perianal abscess formation was observed in 3 patients before the planned date of surgery. One patient experienced spontaneous perforation at the tumor zone prior to surgery.

Perioperative complications: One patient had spontaneous perforation of the colon before surgery. Surgery was complicated in 4 patients with urethra-bladder injury, and in 1 patient with rectal perforation. Temporary nephrostomy tube was inserted in 3 patients. One patient developed incontinence and impotence due to nerve damage caused by bladder injury. Total proctotectomy procedure was performed in 1 patient due to sudden onset of ischemia during mesorectal resection. Perirectal abscesses developed in 2 patients. Surgical complications are shown in Table 3.

Postoperative chemotherapy: Sixteen (53%) patients underwent adjuvant chemotherapy. Chemotherapy was not given to 13 patients with pathologic complete response after surgery or who had preoperative grade Ⅳ toxicity due to CRT. Grade Ⅴ toxicity (sepsis) was seen in only 1 patient after three cycles of chemotherapy. Adjuvant treatment was terminated prematurely in 2 patients due to grade Ⅳ hematologic toxicity.

DISCUSSION

Despite the continuous search for effective multidisciplinary treatment protocols, patients diagnosed with rectum cancer remain a high-risk population for local and distant recurrence. This study provided encouraging results with neoadjuvant HART plus chemotherapy.

A variety of preoperative RT regimens is used in patients with rectum cancer, and conventional RT (45-50 Gy/5 wk) represents the standard regimen for preoperative concurrent CRT. While a statistically significant advantage in terms of local recurrence rates was reported in 14 previous studies examining this regimen, a survival advantage could be shown in only 2 studies for preoperative RT[9,19]. In these studies, patients with early stage disease (I) and no requirement for preoperative CRT represented the majority of the participants. In a Polish study comparing short-term preoperative RT and conventional CRT, a statistically significant superiority of CRT was observed in terms of complete response rates (P < 0.0001); however, no difference was found in local control and survival[20]. In a randomized study from France comparing preoperative RT and CRT, better pathologic complete response rate (11.4% *vs* 3.6%, P < 0.0001) and reduced local recurrence (8% *vs* 16.5%, P < 0.051) were observed in the CRT arm[10]. In the similarly designed EORTC 22921 study, lower local recurrence was demonstrated in the CRT arm (P < 0.001)[21].

Several phase Ⅱ studies administrating HART alone or with concurrent chemotherapy have also been performed[22-28]. In the HART study by Bouzourene *et al*[29] none of the patients had complete response and 8% of the patients had local remission. In another study by Voelter *et al*[23] examining HART and CT, the reported positive circumferential resection margin was 21% and local control was 100%. In our study, radial surgical margin positivity was 7%, and after a median follow-up of 60-mo the local control rate was 97%. Local recurrence was seen in only 1 patient preoperatively staged as T3N1 and the radial surgical margin was pathologically positive in this patient. In contrast with a phase Ⅱ study by Marsh *et al*[26], where 17 patients receiving preoperative capecitabine and HART had a complete response of 18%, the complete response rate was 21% (grade Ⅳ) and the

Table 4 Studies investigating hyperfractionated accelerated radiotherapy regimen for locally advanced rectal cancer

Study	Number of patients	Design	Follow-up (mo)	Total RT dose	Intervals (wk)	Concomitant chemotherapy	pCR[1]	Local control	Down-staging
Coucke *et al*[24] 2006	250	Prospective	39 mo	41.6 Gy/1.6 Gy	1 wk	None	1.20%	91.70%	38%
Ceelen *et al*[22] 2007	50 *vs* 91	Prospective	67 mo *vs* 28 mo	41.6 Gy/1.6 Gy *vs* 45 Gy/1.8 Gy	13 d *vs* 6 wk	None *vs* 5-FU bolus chemotherapy	4% *vs* 18%	94% *vs* 95.6%	30% *vs* 51%
Voelter *et al*[23] 2006	33	Prospective	104 mo	41.6 Gy/1.6 Gy	1wk	CPT-11	NA	100%	33%
Brooks *et al*[42] 2006	20	Prospective	31 mo	25 Gy/1.67 Gy (CHART)	1 wk	None	NA	95%	NA
Widder *et al*[43] 2005	184	Prospective	43 mo	25 Gy/2.5 Gy	1 wk	None	NA	97.90%	NA
Bouzourene *et al*[29] 2003	104	Prospective	40 mo	41.6 Gy/1.6 Gy	1 wk	None	0%	92.30%	43%
Marsh *et al*[26] 2010	17	Prospective	NA	50.4-55.2 Gy/1.2 Gy	4-6 wk	Capesitabine 825 mg/m^2-twice per day	18.80%	NA	81.25%
The present study	30	Prospective	60 mo	42 Gy/1.5 Gy	6-8 wk	5-FU (325 mg/m^2) continuous infusion	21%	96.70%	59%

[1]Pathological complete response; NA: Not available; RT: Radiotherapy; pCR: Pathological complete response.

Table 5 Biological equivalent doses[44]

	Tumor control/acute normal tissue complication probability		Late normal tissue complication probability
	Bed (Gy) (α/β = 10 Gy)		Bed (Gy) (α/β = 3 Gy)
Regimen	No time correction	With time correction	
25 Gy/5 fr/5 d (d = 5 Gy)	37.5	37.5	66.7
50 Gy/25 fr/33 d (d = 2 Gy)	60.0	44.4	83.4
42 Gy/28 fr/18 d (d = 1.5 Gy)	48.3	41.7	63.0

Equation 1: Linear quadratic based isoeffect, basic formula without time correction, BED = nd (1+d/α/β), where *n* = number of fractions, d = dose (Gy) per fraction, α/β = the LQ quotient, Equation 2: Time-corrected LQ- formula, BED = nd (1+d/α/β)-γ/α (T- Tk), where γ/α = repair rate (set to 0.6 Gy/d), T = overall treatment time and Tk = proliferation delay (set to 7 d, or maximally T).

near-complete response rate was 31% (grade Ⅲ) among our participants. Studies with HART regimen are shown in Table 4.

The primary aim of this study was to search for possible therapeutic strategies that may help increase the rate of pathological tumor response and to decrease late side effects. In the regimen examined herein, decreased fraction size and shortened total treatment duration were hypothesized to result in decreased late and early side effects, respectively. Treatment duration and doses were different from those administered in conventional RT schemes. Therefore, a biological effective dose formula was used for dose calculations instead of the given dose, according to a time-corrected linear quadratic model[30,31]. Biological equivalent doses are shown in Table 5.

In this study combining HART and concurrent chemotherapy, 8 patients developed (26.6%) CRT-related grade Ⅲ-Ⅳ toxicity. Although there was an increase in acute reactions, these effects were generally tolerable and RT was completed without interruption in all patients. In 4 patients, chemotherapy was interrupted shortly due to chemotherapy-related acute side effects. Toxicity was increased as a result of combined use of chemotherapy and RT regimen together with a higher chemotherapy dose as compared to conventional chemotherapy. The highest incidence of side effects was observed at weeks 3 and 4, which correspond to the development of acute mucosal side effects.

In addition, there is some literature data available on early side effects in rectum cancer patients treated with neoadjuvant conventional CRT. For example, in the EORTC 22921 study, grade Ⅲ-Ⅳ toxicity occurred in 14% of the patients[21]. In that study, the probable cause of increased side effects was the total treatment duration and impaired tissue repair as a consequence of shorter intervals between fractions of the chosen HART regimen. In a retrospective study where neoadjuvant CRT and HART alone were compared, no grade Ⅲ-Ⅳ toxicity was reported in the HART arm of the study[22]. In the Phase Ⅱ 93-01 study, patients were treated with neoadjuvant HART with no significant increase in acute side effects[32]. In another phase Ⅱ study with preoperative HART and concurrent irinotecan (CPT-11), addition of chemotherapy was associated with an increase in grade Ⅲ-Ⅳ toxicity[23],

while the most common grade Ⅲ-Ⅳ side effects observed in this study included diarrhea (24%) and infection (9%). In that phase Ⅱ study, early side effects were more frequent than in our study. Probably, reduced incidence of diarrhea in this study could be explained on the basis of sparing the bowel volume out of the RT field.

Bowel perforation occurring in 2 of our patients raises the question of whether a period of 4 wk allows adequate time with normal tissue recovery following an intensive therapy regimen with neoadjuvant HART and concurrent chemotherapy. 5-FU is known to affect the repair mechanism in intestinal cells[33] and the 5-FU dose used in this study might have played a role in the development of perforation in 2 of our patients.

The ideal duration between neoadjuvant therapy and surgery remains a source of debate. The objective of early surgery following short-term RT is to reduce or prevent long-term side effects. However, delayed surgery has been reported to result in increased rates of tumor regression and pathological complete response. In randomized studies utilizing short-term preoperative RT, the time between RT and surgery is relatively short[19,34], posing some challenges in the interpretation of the effects of the timing of surgery following RT. Early and delayed surgery were compared in the Stockholm Ⅲ study where local control, DFS and OS were found to be similar in between three arms[35]. In the randomized Istanbul R-01 study examining the ideal timing for surgery after preoperative CRT, no significant associations were observed between the time-to-surgery and regression rates or local control rates. Surgical margin seems to be the most important factor for local recurrence[36].

In our study, no surgery-related deaths occurred (0/29). In a phase Ⅱ study utilizing HART and concurrent CPT-11, the postoperative complication rate was 27%, similar to other neoadjuvant CRT studies[23]. Operative complications were recorded in 7% of the cases in this study. Occurrence of late toxicity only in 1 patient suggests that the strategy of utilizing HART to reduce late toxicity may prove to be successful. While no late side effects were observed in the 91-10 study with preoperative HART[37], in another study comparing conventional CRT with HART alone, late side effects were more frequently observed in the HART arm[22].

In this study, the ability of the HART regimen to achieve a higher tumor regression rate due to decreasing tumor repopulation was examined. In this regard, complete and near-complete response was achieved in 21% and 31% of the participants, respectively. In a previous study comparing HART alone *vs* conventional CRT regimens, lower complete response rates observed in the HART arm underscores the additive effect of chemotherapy[22]. Similarly, in the French and EORTC studies comparing conventional RT and CRT, the reported pathological complete response rates in the CRT arm were 11.4% and 14%, respectively[38,39]. In our study, HART with concurrent chemotherapy was found to achieve complete or near-complete tumor regression in 52% of the patients. Preoperative HART scheme appeared to be capable of increasing tumor response and local control rates, but no difference was found for OS in phase Ⅱ studies[22]. This study showed no survival benefit despite a high pathological response rate. A study by Petrelli *et al*[36,40] and randomized Istanbul R-01 study did not find any correlation between pathological complete response rate and survival.

Circumferential (lateral) margin positivity was found in 2 patients, whereas only 1 patient showed local recurrence during a median follow-up period of 60 mo. Thirteen patients had distant metastases. Extensive hepatic metastases were found in early phase in 3 patients who died due to systemic disease.

In conclusion, earlier studies have proven the feasibility of HART treatment in terms of early and late side effects in this patient population. As in our study, improved local control rates and tumor regression may be achieved with HART but with higher toxicity. Toxicity could be reduced by giving chronomodulated concomitant capecitabine in Brunch Study[41]. A plausible option would be to reduce the dose of 5-FU to reduce toxicity.

ARTICLE HIGHLIGHTS

Research background

Currently, preoperative chemoradiation (CRT) is the preferred treatment regimen in locally advanced rectal cancer patients, owing to low local recurrence rates and higher chance of sphincter-sparing surgery. Besides conventional radiotherapy consisting of 45-50 Gy/1.8-2 Gy/5-6 wk, other radiotherapy schemes are also used. The hyperfractionated accelerated radiotherapy (HART) scheme reduces the risk of repopulation in tumor cells by shortening the treatment time and increases the repair capacity of normal tissues. In this background, a HART scheme and the combination of infusional 5-fluorouracil (5-FU) was examined in this study to augment the pathological complete response.

Research motivation

Local recurrence is still a substantial problem for locally advanced rectal cancers. Investigating tolerability and the effect of different radiotherapy schemes on local control other than conventional and hypofractionated radiotherapy can be a solution.

Research objectives

This study was mainly designed to observe the early and late effects of HART regimen in combination with neoadjuvant chemotherapy in patients diagnosed with locally advanced rectal cancer. The primary aim of this study was to search for possible therapeutic strategies that may help increase the rate of pathological tumor response and to decrease late side effects.

Research methods

Previously untreated locally advanced rectal cancer patients with histological confirmation were included in the study. The patients were clinically staged according to positron emission-computed tomography and pelvic-diffusion magnetic resonance imaging. All patients received preoperative HART (42 Gy/1.5 Gy/18 d/bid) and concurrent continuous infusion of 5-FU (325 mg/m^2) and were hospitalized during treatments to observe the possible acute side effects. Total mesorectal excision was performed 4-8 wk after the completion of chemoradiotherapy. Four cycles of 5-FU (400 mg/m^2, D1-5, q 28 d) plus folinic acid (20 mg/m^2, D1-5, q 28 d) were administered postoperatively. The primary

endpoint was pathological response rate after CRT, and secondary endpoints included the local control rate, surgical margin positivity, survival and toxicity.

Research results

Thirty patients were included between October 2007 and March 2009. The median age was 53 years. Most of the patients clinically staged as T3N+ disease (90%). Surgery was performed at week 4 in half of the patients. Twelve patients (41%) underwent sphincter-sparing surgery. The Dworak total regression scoring system was used to evaluate pathological response, and grade Ⅳ (total) regression was found in 6 of 29 (21%) patients; nine patients (31%) had grade Ⅲ (near total) regression. Positive margins were found in 2 patients (6.6%). One (3.3%) patient had local recurrence during a median follow-up of 60 mo. The 5-year disease-free survival rate was 53%, while the 5-year overall survival rate was 53.1%. There were no interruptions in RT due to toxicity, while in 4 patients chemotherapy was interrupted for 1 wk. Sixteen (53%) patients underwent adjuvant chemotherapy.

Research conclusions

Improved local control rates and tumor regression may be achieved with HART but with higher acute toxicity. Toxicity could be reduced by giving chronomodulated concomitant chemotherapy or reducing the dose of 5-FU. Surgery timing has no effect on survival but still should be considered because of increased acute side effects due to HART fractionation. Besides an increased pathological response rate, this study showed no survival benefit.

Research perspectives

Different HART schemes can be examined with concomitant chemotherapy in the future studies. Because of the high incidence of acute toxicity, fraction dose and chemotherapy doses should be designed properly for new studies.

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