



Hypofractionated Preoperative Chemoradiotherapy In Locally Advanced Rectal Cancer: Preliminary Results

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OBJECTIVE

The aim of the present study was to evaluate the efficacy and safety of preoperative hypofractionated chemoradiotherapy in patients with locally advanced rectum cancer, which was previously observed in the Far East (KROG 11-02).

METHODS

Twenty-seven patients with locally advanced rectal cancer (cT3–4N0–2M0) between November 2014 and August 2016 were included in the study. A 2-week schedule of hypofractionated radiotherapy, 33 Gy/10 fractions, with concurrent 1 cycle of oral capecitabine (1650 mg/m²/day) was applied. Patients were scheduled to undergo surgery 6–8 weeks after completion of chemoradiotherapy. End points were tumor responses and toxicity.

RESULTS

All patients underwent total mesorectal excision except only one patient, and statistical analysis was performed on 26 patients. Of the patients, 10 (38.4%) were downstaged, and 3 (11.5%) had a pathologically complete response. No grade 3–4 toxicity was observed in the patient group. Grade 1–2 hematologic toxicity developed in 2 (8%) patients, and no biochemical abnormality was observed. Gastrointestinal toxicity was observed in 17 (65%), genitourinary toxicity in 8 (30%), and radiodermatitis in 3 (11%) patients. One patient had permanent anastomosis and wound dehiscence, and one patient had presacral abscess. Enterocutaneous fistula developed in only one patient.

CONCLUSION

A 2-week schedule of radiotherapy with oral capecitabine in patients with locally advanced rectal cancer resulted in similar toxicity levels and tumor response rate in comparison with previous results.

Keywords: Capecitabine; hypofractionated radiotherapy; preoperative chemoradiotherapy; rectal cancer.

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Introduction

Currently, neoadjuvant chemoradiotherapy/radiotherapy has become the standard treatment in locally

advanced rectal cancer compared with postoperative modality due to both decreased side effect profile and increased local control and sphincter protection.[1] Long-course chemoradiotherapy (LCCRT, 45–50.4

Gy/25–28f) is the preferred treatment for rectal tumors with extramural spread and/or regional lymph node involvement, especially in the majority of Eastern European countries and in the United States. Short-course radiotherapy (SCRT, 25 Gy/5f), which is more economical and comfortable than long-term treatment, is preferred especially in middle and upper rectum patients without the involvement of the mesorectal fascia, peripheral organ, or regional lymph node in Northern Europe.

Although the most remarkable advantage of LCCRT over SCRT is the increased tumor response, two randomized phase III trials comparing neoadjuvant SCRT and LCCRT indicated no significant difference with regard to local control, disease-free survival, overall survival, organ preservation, and late toxicity rates.[2,3] Additionally, SCRT provides better patient compliance, shorter treatment time, and lower costs than standard fractionation with chemotherapy. Moreover, according to recently published articles, short-term radiotherapy with delayed surgery for >4 weeks provides better pathological outcomes and fewer postoperative complications.[4]

In order to create a better treatment scheme in terms of patient comfort and quality of life, as well as to establish an equivalent treatment plan in terms of treatment efficacy and safety, we used a new protocol that is biologically similar to the standard radiotherapy dose and previously observed by Lee et al.[5] for toxicity profile and reliability. We aimed to prospectively monitor the use of a 2-week schedule of hypofractionated radiotherapy regimen delivered as a total dose of 33 Gy in 10 fractions, with 1 cycle of oral capecitabine in rectal cancer in our patient group in the presence of radiological and pathological data.

Materials and Methods

Patient eligibility

Eligibility criteria were histologically confirmed adenocarcinoma, distal margin of the tumor located <12 cm from the anal verge, cT3–4N0–2 classification as determined by magnetic resonance imaging (MRI) and/or endorectal ultrasonography (EUS), no evidence of distant metastasis, Karnofsky performance score \geq 70, and adequate bone marrow, liver, and renal function. Exclusion criteria were history of radiotherapy or chemotherapy, the existence of serious comorbidity, and fluoropyrimidine sensitivities.

Evaluation

This was a prospective observational study. All patients with resectable locally advanced rectal adenocarci-

noma received preoperative radiotherapy (33 Gy/10f) with 1 cycle of oral capecitabine (1650 mg/m²/day) from November 2014 to August 2016.

For clinical staging, we used clinical history, physical examination, digital rectal examination, carcinoembryonic antigen determination, blood profile, and staging examinations including colonoscopy with biopsy, chest and abdomen computed tomography (CT) scans, endoscopic ultrasound, pelvic MRI, and positron emission tomography/CT. A lymph node size of >1 cm in MRI and/or EUS is considered to be clinically positive.

All patients were clinically staged to determine the pre-treatment and post-treatment stages with the American Joint Committee on Cancer criteria 7th edition. Circumferential radial margin is defined as involvement within a tumor margin \leq 2 mm. The tumor regression grade (TRG) was assessed according to the classification recommended by the Ryan TRG system. [6] Pathologic complete response (pCR) was defined as no visible microscopic disease in the primary tumor.

Patients were seen in the polyclinic two times during the chemoradiotherapy to evaluate acute toxicity and compliance. In addition, patients were monitored 4 weeks after completion of radiotherapy and time to surgery.

Treatment

All patients received pelvic radiotherapy (RT) with concurrent oral capecitabine. Pelvic RT was planned using the Eclipse 10.0 treatment planning system on the Rapid Arc Millennium 120 MLC system using intensity-modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) with a total dose of 33 Gy in 10 fractions. All patients were simulated in the supine position. Fullness or empty bladder was not implemented. RT was delivered to the clinical target volume (CTV), including the entire mesorectum and obturator, presacral, and internal iliac lymph nodes (plus external iliac lymph nodes in the cT4 patients and patients with positive obturator lymph nodes). The planning target volume was symmetrically generated with a 7 mm margin around the CTV. The peritoneal cavity, bladder, and femur heads were the organs at risk. Oral capecitabine was prescribed at a dose of 1650 mg/m²/day only during radiotherapy with drug holidays on weekends, as used in the routine. Patients underwent total mesorectal excision 6–8 weeks after the completion of chemoradiation. The postoperative chemotherapy was at the discretion of the medical oncologist. Figure 1 shows the treatment scheme.

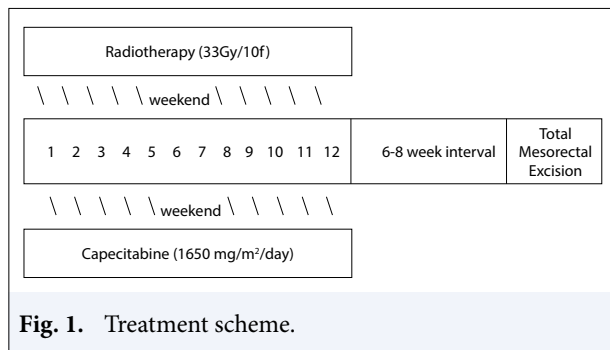


Fig. 1. Treatment scheme.

Statistical analysis

Data were presented as rate for categorical values or mean and median for continuous variables. The clinical and statistical significant correlation between continuous variables was calculated by Spearman's rank correlation test, *r_s* (spearman's correlation coefficient), and *p* value (two-tailed). All statistical data were analyzed using the SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). A *p* value < 0.05 was considered statistically significant.

Results

A total of 27 patients with locally advanced rectal cancer who received preoperative radiotherapy concurrently with oral capecitabine at Okmeydanı Research and Training Hospital were included in the study. One patient was excluded from the analysis due to surgery rejection. Among the 26 patients, there were 12 (46.1%) male and 14 (53.9%) female patients. The mean age of the patients was 58 (51–77) years. The average follow-up time was 22 (7–37) months. According to pre-treatment staging, 23 (88.4%) patients had cT3 lesions, and 3 (11.6%) patients had cT4 lesions. In addition, at the time of diagnosis, 20 patients had clinically node-positive disease. The clinical and pathological characteristics of all patients are shown in Table 1. Although all patients received the prescribed doses of oral capecitabine and radiotherapy, treatment of five patients was extended by 1 to 2 days due to malfunction of the Rapid Arc.

The median interval between completion of chemoradiotherapy and surgery was 56 (min 36–max 88) days. Twenty-four (92.3%) patients underwent low anterior resection including two patients who had tumor within ≤ 2 cm to anal verge. There were three patients in the sphincter-saving R1 resection group and one patient in the abdominoperineal resection R1 group. Ten (38.4%) patients were downstaged. Three (12%) patients had

Table 1 Patient characteristics

Characteristic	N=26 (%)
Gender	
Female	14 (53.8)
Male	12 (46.2)
Differentiation	
Well	7 (26.9)
Moderate	15 (61.5)
Poor	3 (11.5)
Tumor distance from the anal verge (cm)	
0-2cm	4 (15.3)
2-5cm	8 (30.7)
>5cm	14 (53.8)
Median age	Median (range): 58 (51-77)
Pre CRT CEA ng/ml	Median (range): 4.5 (0.9-29)
cT stage	
T3	23 (88.4)
T4	3 (11.6)
cN stage	
N0	5 (19.2)
N1	4 (15.3)
N2	17 (65.3)
CRM	
Positive	6 (%23)
Negative	21 (%77)

CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; CRM, circumferential margin

Table 2 Acute toxicity of the preoperative treatment

Adverse Events	N=26 (%)	
	Grade 1-2	Grade 3-4
Hematologic		
Leucopenia	2 (%7.6)	-
Anemia	2 (%7.6)	-
Thrombocytopenia	-	-
Non-hematologic		
Diarrhea	14 (%53.8)	-
Dysuria	8 (%30.7)	-
Radiodermatitis	3 (%11.5)	-
Nause, vomiting	5 (%19.2)	-

pathologic complete response after preoperative therapy (ypCR). Of the patients, 6 (23.1%) had TRG1 with total tumor regression and single cells or small groups of cancer cells, 14 (53.8%) had TRG2 with residual cancer outgrown by fibrosis, and 6 (23.1%) had TRG3 with significant fibrosis outgrown by cancer and no fibrosis with extensive residual cancer. Three patients did not

receive adjuvant chemotherapy due to comorbidity, treatment rejection, and surgical morbidity.

Early and late side effects that occurred during and within 1 month after chemoradiotherapy are listed in Table 2. There was no grade 3–4 toxicity observed in the patient group. Grade 1–2 hematologic toxicity (leukopenia, anemia, and thrombocytopenia) developed in 2 (8%) patients, and no biochemical abnormality was observed. Grade 1–2 gastrointestinal toxicity (diarrhea, nausea, vomiting, and abdominal pain) was observed in 17 (65%), genitourinary toxicity in 8 (30%), and radiodermatitis in 3 (11%) patients, respectively. One patient had permanent anastomosis and wound dehiscence, and one patient had presacral abscess. Enterocutaneous fistula developed in only one patient.

Discussion

The most common regimens are SCRT (five fractions of 5 Gy over 1 week) and LCCRT with a conventional dose of 1.8–2 Gy/fraction for a total dose of 45–50.4 Gy combined with 5-Fu-based chemotherapy; however, in different geographical regions, such as Japan and China, there are different hypofractionated regimens that had been tested in previous studies applied except for the conventional dose of neoadjuvant radiotherapy in rectal cancer.[5,7,8] The aim of this trial was to evaluate the efficacy and safety of hypofractionated chemoradiotherapy, which was previously observed by Lee et al., in our patient group.[5] While downstaging of the TNM stage and pCR were evaluated as efficacy, tolerability and toxicity profile were assessed as safety.

In this trial, downstaging was observed in 10 (38%) patients. Three (12%) patients had ypCR, and a total of 6 (23.1%) patients had ypCR with minimal tumor cells in fibrosis at the final pathology. As a result, we achieved to obtain comparable results with Lee et al.[4] that had 13.8% ypCR and 33.8% downstaging.[5] In comparison with the results of previous studies, this regimen appears to be equal to preoperative chemoradiotherapy protocols that further increased the pCR rate to approximately 11% to 18%.[9–12] In addition, there are various studies in which SCRT with delay surgery had been tested to increase the pCR rates.[4,13] Two randomized studies that compared SCRT with immediate surgery and SCRT with delayed surgery reported a higher rate of pCR in the delayed surgery group.[14,15] In another randomized trial, the comparison of SCRT and delayed surgery with LCCRT showed a higher rate of pCR in the chemoradiation groups (3% vs. 13%).[16] Additionally, in the literature,

there are also some studies that had tested SCRT, followed by consolidation chemotherapy before surgery. Bujko et al. stated that SCRT, followed by 3 cycles of FOLFOX (5-fluorouracil, oxaliplatin, and leucovorin) chemotherapy in comparison with long-course oxaliplatin-based preoperative chemoradiation, reveals a higher pCR rate in the SCRT group (21% vs. 8%).[17] In addition, Myerson et al. used a regimen of five fractions of pelvic radiation therapy, followed by 4 cycles of FOLFOX evaluated as a preoperative regimen for cT3–4 rectal cancer. There were a total of 21 (28%) ypT0 including 19 (25%) ypT0N0 complete response.[18]

Acute toxicity during SCRT is most often of grade 1–2. However, in most of the post-radiation toxicity in the immediate surgery group, operation occurs before the occurrence of acute post-radiation toxicity, and more side effects were seen when surgery was delayed. In the interim analysis of the Stockholm III randomized trial, severe acute toxicity was reported in 4.2% of the patients in the SCRT and delayed surgery groups and in none of the patients in the immediate surgery group. [4] Nevertheless, SCRT with delayed surgery showed a significant lower incidence of postoperative complications than percutaneous stereotactic radiotherapy with immediate surgery (39.4% vs. 52.5%), and long-course radiotherapy caused prolonged treatment time with similar results.[14] Yeo et al. (KROG 10-01) reported that only one study performed short-course radiation concurrently combined with 5-Fu and leucovorin, followed by surgery 4 to 8 weeks later. The pCR rate was only 1.4%, and the acute grade 3–4 toxicity was 38%. [19] In the present study, the most common side effect was grade 1–2 gastrointestinal toxicity observed in 17 (65%) patients. Although this toxicity was slightly higher than the literature, there were no grade 3–4 toxicity and no toxicity-related treatment break.

In the present study, a 2-week scheduled chemoradiotherapy with oral capecitabine showed very low toxicity profiles similar to Lee et al.[5] Probably the shortened duration of treatment with 1 cycle of capecitabine prevented to detect more acute toxicity. Compared with the main study, toxicity profiles were similar, but any grade 3 toxicity was not observed in our study. That can be caused by a small number of patients or using highly conformal radiotherapy technologies as IMRT or VMAT in comparison with the standard three or four field box technique. Nowadays, especially developing technologies provide the opportunity for more reliable implementation of more intensive treatment modalities. Radiotherapy applied with technologies, such as IMRT or VMAT, compared with previous series, can

be reduced acute bowel toxicities by decreasing the radiation exposure of the small bowel.[20] Although the distinct advantage of IMRT in intestinal doses is shown in dosimetric studies, additional research is needed to determine whether IMRT is able to reduce the side effects during and after pelvic RT with hypofractionated radiotherapy.[21,22]

Short-term radiation has been reported to lead to late intestinal obstruction and sexual dysfunction.[23] Hereby, instead of acute toxicity for hypofractionated radiotherapy, the risk of long-term complications raises doubt on reliability.[24-26] Therefore, concern regarding late toxicity due to hypofractionated schedule can be a significant deterrent for physicians. A 2-week course of preoperative chemoradiotherapy achieved a satisfying downstaging rate and low incidence in toxicity profiles, considering that the late effects of 33 Gy in 10 fractions are similar with 25 Gy in 5 fractions. According to the linear-quadratic model, assuming that a/b is 3 Gy at the late effect, biologically effective doses were 69.3 Gy³ and 66.7 Gy³, respectively.

Conclusion

Hypofractionated chemoradiation regimen with 33 Gy in 10 fractions with oral capecitabine, followed by delayed surgery for preoperative treatment of rectal cancer, provided a favorable downstaging rate and tolerable toxicity profiles. Therefore, we need to conduct long-term oncological outcomes and phase III trials with larger patient groups.

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Conflict of Interest: None declared.

Ethics Committee Approval: This study was conducted in accordance with local ethical rules.

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