

# Chemoradiotherapy Followed by Surgery in Rectal Cancer: Improved Local Control Using a Moderately High Pelvic Radiation Dose

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**Background:** To determine complete resection and sphincter preservation rates, down-staging, local control and survival associated with concurrent chemoradiotherapy (CCRT) using a moderately high pelvic radiation dose before surgery in rectal cancer.

**Methods:** Fifty-seven patients with histologically proven adenocarcinoma of the mid to lower rectum were treated using preoperative CCRT and surgery. Median radiation dose to the pelvis was 5400 cGy (5040–5580 cGy). CCRT was administered during the first and fifth weeks of radiotherapy with bolus intravenous 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup>/day and leucovorin (LV) 20 mg/m<sup>2</sup>/day for 5 days. Surgery was attempted 4–8 weeks after completing preoperative CCRT. Post-operative chemotherapy was then added for up to four cycles of intravenous 5-FU and LV.

**Results:** Toxicities during CCRT were generally mild and manageable: Grade 1/2 anemia, 3.5%; Grade 1/2 leukopenia, 45.6%; Grade 3 leukopenia, 3.5%; Grade 1/2 diarrhea, 22.8%; Grade 1/2 abdominal discomfort, 7%; and perianal skin reaction, 5.3%. No late complication requiring surgical intervention occurred. Complete surgical resection with a negative resection margin was achieved in 98.2% of patients, and the down-staging rate was 52.6% (30/57; 95% CI 39.6–65.6%). Complete pathologic response was obtained in 5.3% patients (3/57; 95% CI 0–11.1%) and in other 2 patients only sporadic tumor cells nests were noted in surgical specimens. The sphincter preservation rate was 77.2% (44/57; 95% CI 66.3–88.1%). Of 30 patients with tumors located within 5 cm from the anal verge, sphincter preservation was possible in 18 patients (60.0%; 95% CI 47.3–72.7%). With a median follow-up duration of 40 months, overall and disease-free survival (DFS) rates over 3 years were 91.8% (95% CI 85.5–98.2%) and 79.7% (95% CI 71.2–88.2%), respectively. At univariate analysis, significant factors for DFS was LN involvement status ( $P = 0.024$ ). Local and distant failure rates over the same period were 5.3 and 21.1%, respectively.

**Conclusions:** Preoperative CCRT produced encouraging down-staging rates and was found to facilitate complete resection and sphincter saving in distal rectal cancer with acceptable toxicity. Further studies are warranted using this moderately high radiation dose to the pelvis to improve the local control.

*Key words:* rectal cancer – surgery – chemoradiotherapy

## INTRODUCTION

A general consensus has been reached regarding the role and effectiveness of preoperative concurrent

chemoradiotherapy (CCRT) in the management of locally advanced rectal cancer, and it is known that preoperative CCRT, as opposed to postoperative CCRT, improves local control and reduces overall treatment-associated toxicities (1–3). Moreover, the benefits of preoperative radiotherapy (RT) are known to be more highly correlated with increased radiosensitivity relating to the intact vasculature and higher oxygen pressure in the radiation field than postoperative

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radiotherapy (4). In addition, it has been reported that a short-term regimen of high-dose (25 Gy in five fractions) preoperative RT increases resectability, sphincter preservation and local control in locally advanced rectal cancer (5), and consecutive studies (6–8) demonstrated that preoperative CCRT is better than preoperative RT alone in terms of tumor response and local control in locally advanced rectal cancer. Currently, preoperative CCRT is generally regarded as a standard therapy for locally advanced rectal cancer, which increases resectability, sphincter preservation, local control and possibly survival. However, many patients continue to lose the anal sphincter and experience local recurrence after preoperative CCRT. Thus, we introduced a presurgical RT scheme based on a moderately high radiation dose to increase sphincter preservation and improve local control. The rationale for this approach originated from reports that higher radiation doses improve response and local tumor control in other locations (9,10).

The present study was designed to evaluate the association between radiation dose and complete resection, sphincter preservation, down-staging rates, local control, disease-free survival (DFS) and overall survival (OS) and treatment feasibility in rectal cancer patients treated with CCRT using a moderately high pelvic radiation dose followed by surgery.

## PATIENTS AND METHODS

### ELIGIBILITY

Inclusion criteria for this study were as follows: (i) biopsy-proven adenocarcinoma of the rectum, (ii) age 75 years or younger, (iii) Eastern Cooperative Oncology Group performance status score of  $\leq 2$ , (iv) preoperative TNM stage II–III (T1–4, or N positive and M0) on computerized tomography (CT) scanning and (v) granulocyte count  $> 3000/\text{mm}^3$ ; platelet count  $> 100\,000/\text{mm}^3$ ; hemoglobin concentration  $> 10\text{ g/ml}$ ; serum creatine value not  $> 1.5\text{ mg/ml}$ ; age  $\geq 18$  years. Informed consent was obtained from all patients.

### PRETREATMENT EVALUATION

Medical history and physical examination including digital rectal examination, serum biochemical tests, complete blood count, tumor marker (carcinoembryonic antigen (CEA)) study, chest X-ray, colonoscopy and abdomino-pelvic CT were included for the pretreatment evaluation.

Clinical stage was determined according to abdominal CT and rectal examination using the American Joint Committee on Cancer TNM cancer staging, the criteria were as follows: tumor extending into peritoneal fat was defined as T3, tumor invading surrounding structures was defined as T4 and short diameter of lymph node beyond 1 cm was defined as node positive.

## PREOPERATIVE CHEMOTHERAPY AND RADIOTHERAPY

### CHEMOTHERAPY

5-Fluorouracil (5-FU)  $400\text{ mg/m}^2/\text{day}$  and leucovorin (LV)  $20\text{ mg/m}^2/\text{day}$  for 5 days on Days 1–5 and 29–33 during RT were delivered with continuous infusion as preoperative chemotherapy regimens. All 57 patients received the preoperative chemotherapy. Postoperative adjuvant chemotherapy was then added for up to four cycles of intravenous 5-FU and LV.

### RADIOTHERAPY

Pelvic RT was delivered with a three-field technique using megavoltage linear accelerator (6–10 MV). All patients were simulated in prone position with rectal barium and an anal marker. To visualize the small bowel for displacing of it, each patient was instructed to drink oral contrast solution 2 h before the simulation. The superior border of the whole pelvis was placed at the lumbosacral junction. The inferior border was placed at  $> 3\text{ cm}$  caudal to the gross tumor. The lateral field border extended 1.5 outside the bony pelvis. The anterior border of lateral fields was  $\sim 3\text{ cm}$  anterior to the gross tumor and shaped to include the internal iliac lymph nodes, and the posterior border of lateral fields extended to encompass all the sacral vertebra. A three-field treatment plan composed of a 6-MV photon posterior–anterior field and a 10-MV photon opposed lateral field with wedges of  $45^\circ$  was planned. The beam weights of the three-field were adjusted by considering the dose distribution. All patients received a dose of 45 Gy over 4(1/2) weeks in fractional doses of 1.8 Gy to the whole pelvis. And then, an additional boost of 9 Gy for a total of 54 Gy was given to the gross tumor volume (GTV). The GTV for RT was defined in accordance with the International Commission on Radiation Units and Measurements Report 50. The prescription dose was specified at the isocenter of the GTV. Median total radiation dose to pelvis was 54 Gy (50.4–55.8 Gy). During the treatment, patients were examined weekly for assessing acute toxicity. Acute toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) acute scoring system (11). The Grade 1–4 toxicity was determined based on the patients' symptoms and signs.

### FOLLOW-UP EVALUATION

Follow-up evaluation was done with 3 months intervals for 2 years and then twice a year for 3 years after surgery. Rectal examination, imaging (including chest X-ray, liver ultrasonography, CT of the abdomen and sigmoidoscopy) and biochemical tests (including CEA) were performed at the time of evaluation. Local recurrence was defined as those originating in the primary tumor area, pelvic side wall,

regional lymph node and pelvis. All other recurrences were considered distant metastasis.

#### STATISTICAL ANALYSIS

The rates of local recurrence and distant metastasis were to be analyzed for the patients followed up between 16 and 87 months after surgery. Response and toxicities were shown by descriptive methods. The OS was defined as the interval between the initiation point of preoperative CCRT and the date of the last follow-up point or death. Disease-free survival was defined as the interval between the initiation point of preoperative CCRT and the date of the last follow-up point, death or any type of events (including local and distant recurrence). The endpoints of the study were OS, DFS, local and distant metastasis. The OS and DFS curves were constructed according to the Kaplan–Meier method (12). The impact of clinicopathologic factors (age, sex, operation method, tumor size, lymph node involvement and stage) on DFS and OS was examined. The analyses of DFS and OS for these factors were carried out by the Kaplan–Meier method, and the evaluation of differences was performed with the log-rank test. To find the factors predictive for OS and DFS after preoperative CCRT, the Cox proportional-hazards model (13) was used to calculate hazard ratios and 95% confidence intervals in the multivariate analyses. A two-sided  $P \leq 0.05$  was considered statistically significant. The SPSS software package (version 11.0; SPSS Inc., Chicago, IL, USA) was used to analyze the data.

## RESULTS

#### PATIENTS CHARACTERISTICS

Between January 1999 and December 2004, 57 patients with locally advanced rectal cancer were enrolled in this study. The characteristics of these patients are summarized in Table 1.

#### SURGICAL PROCEDURES AND MORBIDITIES

The median interval time between completion of preoperative CCRT and surgery was 5.7 weeks (range, 4.4–8.3 weeks). Complete resection with negative resection margin was confirmed in 56 patients (98.2%). The type of surgery was determined according to tumor and other individual variables. Thirty-five lower anterior resection, 7 extreme lower anterior resection and 13 abdominoperineal resection and 2 Hartmann's procedure were performed (Table 2). Forty-two patients (63.2%) received LAR; of which, 24 patients (57.1%) received LAR with ileostomy or colostomy, and 18 (75%) of these 24 underwent an ileostomy or colostomy repair operation. Therefore, in our study, 63.2% (18 + 18/57) of patients did not undergo colostomy, including 18 patients who received LAR alone. Total mesorectal excision (TME) with lymph node dissection was done in all patients.

**Table 1.** The clinical characteristics of the 57 patients

Variables	Number of patients (%)
Age	
Median	55
Range	35–71
Sex	
Male	47 (82.5)
Female	10 (17.5)
Performance status	
0–1	57 (100)
2–4	0 (0)
Tumor location	
Lower (<5 cm)	30 (52.6)
Mid (5–10 cm)	26 (45.6)
Upper (>10 cm)	1 (1.8)
Clinical stage	
T1–2 N0	2 (3.5)
T3 N0	16 (28.1)
T3 N1	39 (68.4)

**Table 2.** Types of surgical procedures and morbidity

	Number of patients (%)
Surgical procedures	
Abdominoperineal resection	13 (22.8)
Lower anterior resection	35 (61.4)
Extreme lower anterior resection	7 (12.3)
Hartmann's procedure	2 (3.5)
Morbidity	
Wound infection	1 (1.8)
Anastomic leakage	1 (1.8)
Pelvic abscess	1 (1.8)
Adhesive ileus	5 (8.8)
Anastomic stricture	3 (5.3)
Rectovaginal fistula	1 (1.8)

The most common postoperative complications were adhesive ileus, 8.8% (5/57), anastomic stricture, 5.3% (3/57), and anastomic leakage 1.8% (1/57). Most cases of adhesive ileus were relieved under conservative management (Table 2).

#### ACUTE TOXICITY DURING CCRT

There was no treatment-related mortality and the morbidity acceptable. During the CCRT, Grade 1–2 diarrhea was

developed in 22.8% (13/57). Grade 1–2 hematologic toxicities during the preoperative CCRT included anemia, 3.5% (2/57), leukopenia 45.6% (26/57), and Grade 3–4 leukopenia was also developed in 3.5% (2/57) (Table 3). Grade 1–2 other toxicities included perianal skin reaction, 5.3% (3/57), bowel movement 7% (4/57) and tenesmus 10.5% (6/57). There were no chronic toxicities which required the abdominal operation and severe perioperative complications which require major intervention.

#### SPHINCTER PRESERVATION AND TUMOR RESPONSE

##### SPHINCTER PRESERVATION

The sphincter preservation rate was 77.2% (44/57; 95% CI, 66.3–88.1%) for the all patients. Among 30 patients with tumors located within 5 cm from anal verge, sphincter preservation was possible in 18 patients (60.0%; 95% CI, 47.3–72.7%). Of the 18 patients (60.0%) in whom 77.8% (14/18) underwent LAR with ileostomy or colostomy. Of these, 85.7% (12/14) received ileostomy or a colostomy repair operation. No patient required pelvic exenteration for curative resection. Among 30 patients with tumors located within 5 cm from the anal verge, the median distal resection margin was 1.9 cm (range, 0.4–10 cm) after preoperative CCRT. However, the median distal resection margin was 2.6 cm (range, 0.1–6.5 cm) among 27 patients with tumors located at 5–11 cm from the anal verge.

##### TUMOR RESPONSE

**Pathologic Response Rate.** In three patients, complete disappearance of the primary tumor was observed on the pathology specimen. Therefore, the pathologic complete response rate (pCR) was 5.3% (3/57; 95% CI, 0–11.1%). However, as one of the pCR patients had residual tumor cells in a lymph node, complete tumor disappearance in both the rectum and lymph nodes was found in 2 (3.5%) patients.

**Table 3.** Incidence of treatment-related acute toxicity

Toxicity	Acute toxicity <sup>a</sup> (%)		
	Grade 1/2	Grade 3/4	Total
Anemia	3.5 (2/57)	—	3.5 (2/57)
Leukopenia	45.6 (26/57)	3.5% (2/57)	49.1 (28/57)
Perianal skin reaction	5.3 (3/57)	—	6.0 (3/57)
Bowel movement	7.0 (4/57)	—	7.0 (4/57)
Tenesmus	10.5 (6/57)	—	10.5 (6/57)
Diarrhea	22.8 (13/57)	—	22.8 (13/57)

<sup>a</sup>According to the RTOG-EORTC late radiation morbidity scoring scheme.

There were other two patients whose residual primary tumors were microscopic ( $\leq 2$  mm in the greatest dimension). Therefore, the clinical complete response rate was 8.8% (3 + 2/57), and 41 (79.1%) patients had no tumor cells in their lymph node specimen.

**Stage Changes.** The pathologic stage was lower than the initial clinical stage for the Tumor (T) down-staging and nodal (N) down-staging categories, respectively. Comparing the clinical stage with the pathologic stage, the total down-staging was observed in 30 patients (52.6%; 95% CI, 39.6–65.6%). T down-staging was detected in 9 (15.8%) patients, and N down-staging was detected in 27 patients (47.4%). Both T and N down-stagings were observed in 4 (7%) patients. There was no T and N down-stagings in 26 (45.6%) patients, whereas up-staging was also observed in 9 (15.8%) patients (Table 4).

#### FACTORS PROGNOSTIC FOR DFS AND OS

The influence of clinicopathologic features on DFS was analyzed. At univariate analysis, statistically significant factors for DFS were type of surgery ( $P = 0.022$ ) and LN involvement status ( $P = 0.024$ ). Three-year DFS for patients with pathologic node negative was 87.3%, whereas the corresponding 3-year survival for patients with pathologic node positive was 60.2% (Fig. 1). However, the type of surgery did not show significance when excluding two patients receiving Hartmann procedure ( $P = 0.534$ ). The stage showed marginal significance ( $P = 0.064$ ) to influence on DFS. However, age ( $P = 0.844$ ), gender ( $P = 0.350$ ), tumor location ( $P = 0.240$ ) and tumor size ( $P = 0.221$ ) had no

**Table 4.** Patterns of T, N stage change following CCRT

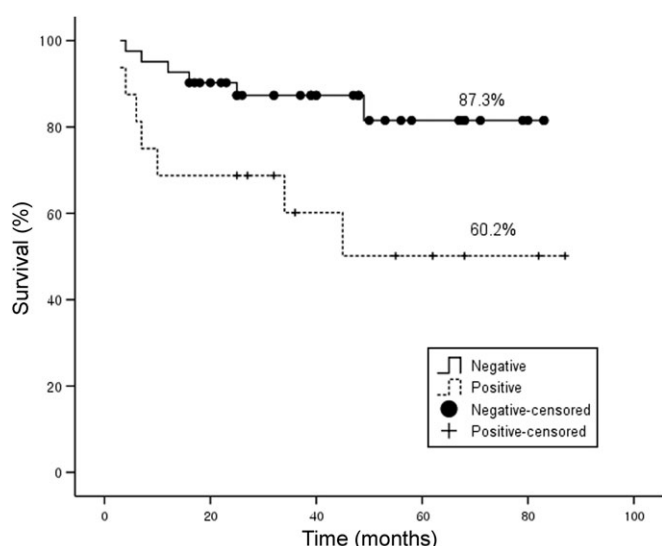
Clinical Stage (n*)	Pathologic Stage (n)
T2 (2)	Tis (1) T0 (1)
T3 (55)	Tis (1) T0 (2) T1 (1) T2 (3) T3 (48)
N0(18)	N0 (41: 14 <sup>†</sup> + 27 <sup>‡</sup> )
N1(39)	N1 (10: 3 <sup>†</sup> + 7 <sup>‡</sup> ) N2 (6: 1 <sup>†</sup> + 5 <sup>‡</sup> )

n, number of patients; thick arrow, down or same staging; dotted arrow, up-staging. CCRT: concurrent chemoradiotherapy

<sup>†</sup>Number of N0 patients.

<sup>‡</sup>Number of N1 patients.





**Figure 1.** Disease-free survival according to nodal status.

influence on DFS. At multivariate analysis, there were no prognostic factors for DFS (Table 5). In the present study, a separate analysis of prognostic factors (age, gender, stage, tumor location, differentiation, resection margin status, tumor size and lymph node) for local recurrence was performed. By univariate analysis, tumor location was identified as being marginally significant ( $P = 0.064$ ). Age ( $P = 0.411$ ), gender ( $P = 0.227$ ), stage ( $P = 0.227$ ), tumor size ( $P = 0.536$ ), tumor differentiation ( $P = 0.689$ ), LN involvement ( $P = 0.105$ ) and distal resection margin ( $P = 0.417$ )

were not found to be significant prognostic factors of local recurrence. By multivariate analysis, no significance was found for any prognostic factor in terms of local recurrence. The influence of clinicopathologic features on OS was also analyzed. At univariate analysis, the type of surgery was the marginally significant factor ( $P = 0.054$ ). Age ( $P = 0.163$ ), gender ( $P = 0.948$ ), location ( $P = 0.647$ ), tumor size ( $P = 0.919$ ), LN involvement ( $P = 0.461$ ) and stage ( $P = 0.359$ ) were not statistically significant prognostic factors for OS. At multivariate analysis, there were also no statistically significant prognostic factors for OS [age ( $P = 0.901$ ), gender ( $P = 0.775$ ), location ( $P = 0.622$ ), type of surgery ( $P = 0.354$ ), tumor size ( $P = 0.943$ ), LN involvement ( $P = 0.885$ ) and stage ( $P = 0.999$ )].

#### THREE-YEAR FOLLOW-UP SURVIVAL AND LOCAL RECURRENCE

A total of 74 patients treated from January 1999 through December 2004 were planned for this study with preoperative CCRT followed by TME. Of 74 patients, 17 patients did not receive all planned treatment course (refusal, 6; disease progression, 6; transfer to other hospital, 5). The study group composed of 47 men and 10 women. The median follow-up is 40 months (range, 16–87 months) at the time of analysis. The overall 3-year survival rate was 91.8% (95% CI, 85.5–98.2%) and the 3-year DFS rate 79.7% (95% CI, 71.2–88.2%). Local recurrence after resection occurred in 5.3% (3/57). Of these recurrences, one occurred in the pre-sacral space and two occurred in the rectal stump and distant metastasis occurred in 21.1% (12/57). Distant metastasis

**Table 5.** Factors associated with disease-free survival in 57 rectal cancer patients

Variable	Univariate analysis		Multivariate analysis	
	HR (CI)	<i>P</i> value	HR (CI)	<i>P</i> value
Age (<50 versus $\geq 50$ )	1.12 (0.37–3.43)	0.844	1.75 (0.44–6.90)	0.427
Gender (male versus female)	0.38 (0.05–2.91)	0.350	0.53 (0.07–4.28)	0.554
Location (5 versus 5–11 cm)	0.51 (0.17–1.56)	0.240	0.98 (0.23–4.11)	0.979
Type of surgery		0.022		0.970
LAR	1			
APR	0.62 (0.14–2.83)	0.535	0.54 (0.09–3.16)	0.493
Hartmann	23.3 (2.27–282.2)	0.009	15.8 (1.07–233.6)	0.044
Tumor size (<5 versus $\geq 5$ cm)	2.24 (0.62–8.16)	0.221	1.84 (0.31–10.81)	0.498
Nodal involvement [(–) versus (+)]	3.52 (1.18–10.49)	0.024	20.0 (0.34–1172.1)	0.149
Pathologic stage		0.064		0.488
0	1			
I	0.00	0.984		0.985
II	0.72 (0.08–6.21)	0.766	0.79 (0.07–8.40)	0.849
III	2.18 (0.26–18.19)	0.472	0.10 (0.01–1.96)	0.129
IV	19.6 (1.01–379.5)	0.049		

HR, hazard ratio; CI, confidence interval.

sites were as follows: lung 6 (42.9%), liver 4 (28.6%), bone 2 (14.3%), skin 1 (7.1%) and brain 1 (7.1%) patient.

## DISCUSSION

Of the treatment modalities available for resectable rectal cancer, preoperative CCRT is widely used to treat locally advanced rectal cancer to increase resectability, and to enhance sphincter preservation, local control and, possibly, survival rates. Faced with the problem of determining radiation dose for preoperative RT, a radiation dose of 45 Gy to the whole pelvis plus a boost median dose of 9 Gy was administered in the present study. This radiation dose was determined using the dose-efficiency concept (14), which is based on a lower rate of local recurrence when a radiation dose similar to that used postoperatively is administered preoperatively instead. Early programs (15,16) on preoperative RT employed low-dose regimens (15) and intensive short-term radiation course (16). In 1964, the Veterans Administration Surgical Adjuvant Group (VASAG) initiated a large-scale, controlled, randomized protocol to study the role of low-dose preoperative irradiation (20–25 Gy in 10 fractions over 12 days) in recto-sigmoid cancer patients (15). In addition, the Stockholm Rectal Cancer Study Group (SRCCG) conducted a controlled clinical trial of radiotherapy (25 Gy over 5–7 days) prior to surgery, compared with surgery alone (16). This short-term regimen of high-dose preoperative RT has been demonstrated to benefit local control and survival (5).

Theoretically, high-dose preoperative RT is capable of sterilizing peripheral areas of tumors and microlymphatic-associated disease, and it has been suggested that high-dose preoperative RT may be capable of sterilizing peripheral tumor areas and microlymphatic disease, and of overcoming the technical difficulties of obtaining tumor-free distal and circumferential margins. However, few studies show a clear dose-efficiency correlation. Fortier et al. (17) reported a dose response, with 67% local control at 40 Gy and 91% local control at 50 Gy without significantly increased toxicities. Ahmad et al. (18) also reported a local recurrence rate of 20% in a low-dose group (45 Gy) and of 8% in a high-dose group (55 Gy). Moreover, Gerard et al. (19) reported that the effect of contact X-ray (CXR) with external beam radiotherapy (EBRT) showed a 24% complete clinical response rate in a group that received a combination of EBRT and CXR versus 2% clinical response rate in a group that received EBRT alone. In particular, the EBRT and CXR groups were able to receive a CXR boost at a mean dose of 85 Gy (range, 50–135 Gy) without significant morbidity. Mohiuddin (20) examined the impact of dose time factors on pCR following preoperative CCRT, and reported that pCR occurred in 44% (8/18) patients who received a radiation dose of  $\geq 55$  Gy and in 13% (2/15) patients who received  $\leq 50$  Gy ( $P = 0.05$ ). Recently, Kirsty et al. (21) reported a trend toward increased pCR at higher doses and a statistically significant increase in

local recurrence-free survival, DFS and OS for radiation doses of  $\geq 46$  Gy.

The primary objectives of our study were to assess acute toxicity and response rate, and the secondary objectives were to analyze survival and failure patterns. In the present study, two cases of T2N0 were enrolled in the response and survival analysis. The rationale for performing preoperative CCRT in these patients was that tumors were located in the lowest portion of the rectum. Thus, LAR after preoperative CCRT did not involve the anus. The initial staging work-up of these two patients was done by physical examination and pelvic CT. As a result of staging work-ups, T3 stage was suspected in both of these patients, but they were enrolled as T2 patients. Nevertheless, we cannot exclude that they had T3 disease, because pelvic CT can understage such patients (22). Furthermore, a recent report (23) suggested that for patients with cT2N0 distal rectal cancer who require APR, preoperative pelvic radiation improves sphincter preservation without apparently compromising local control or survival. Accordingly, we enrolled these two patients in the response and survival analysis. The preoperative CCRT was found to be well tolerated by most patients, and treatment compliance was generally good. Grade 1–2 acute toxicities were: diarrhea, 22.8% (13/57); anemia, 3.5% (2/57); leukopenia, 45.6% (26/57); perianal skin reaction, 5.3% (3/57); bowel movement, 7% (4/57) and tenesmus, 10.5% (6/57) patients. These overall toxicities are comparable with those reported by previous studies (24,25). Similarity toxicities were reported by Vincenzo et al. (22). Their Grade 1–2 acute toxicities were: gastrointestinal, 40%; skin reaction, 30%; and hematologic toxicity, 52%. No patient had Grade 4 toxicity and only 2 (5%) patients developed Grade 3 hematologic toxicity. We prescribed continuous infusion of 5-FU (300 mg/m<sup>2</sup>/day) and LV (20 mg/m<sup>2</sup>/day) for 5 days on Days 1–5 and 29–33 during RT. Whereas, they prescribed 5-FU (1000 mg/m<sup>2</sup>/day) for 5 days on Days 1–5 and days 29–33 post-RT start and cisplatin (60 mg/m<sup>2</sup>/day) on Days 1 and 29 and a pelvic dose 45 Gy plus a booster dose of 5.4 Gy to the primary tumor. Grann et al. (25) prescribed a total dose of 50.4 Gy of radiation to the primary tumor, and reported an overall Grade 3–4 acute toxicity rate of 25% (Grade 3–4 leukopenia 12% and Grade 3 diarrhea 13%). They administered with bolus intravenous 5-FU (325 mg/m<sup>2</sup>/day) plus LV (20 mg/m<sup>2</sup>/day) for two cycles on Days 1–5 and 29–33 of RT. These treatment variabilities appear to be why direct comparisons between these studies and the present study are difficult.

After preoperative CCRT, digital rectal examination was performed in conjunction with colonoscopy. In some patients, the digital assessment of the tumor location from the anal verge was possible. However, in most patients, the precise assessment of the distance of the tumor from the anal verge was imprecise because of the difficulty in differentiating the residual tumor and scar changes due to marked fibrosis or necrotic tissue as a result of the disappearance of the gross tumor after CCRT.

In our study, the 1–2 cm safety margin of each patient was determined, based on post- and pre-CCRT tumor locations. To determine the safety and optimal distal margin of resection in surgery for each patient, we considered previously published reports (26,27) which concluded that a distal resection margin extent of <1 cm has no statistical effect on local recurrence and, thus, that a distal resection margin of 1 cm from a tumor is appropriate clearance for most rectal cancers.

In the present series, the sphincter preservation rate was 77.2% (44/57). Of 30 patients with tumors located within 5 cm of the anal verge, sphincter preservation was possible in 18 (60.0%) patients. However, of the 24 patients who underwent LAR with ileostomy or colostomy, 2 patients (14.3%) could not undergo colostomy repair surgery because of anastomotic leakage or rectovaginal fistula. In our study, 63.2% of patients did not undergo colostomy. No ileostomy or colostomy repair operation could be performed in six patients because of the following reasons: radiation proctitis (2), adhesive ileus (1), rectovaginal fistula (1), anastomotic leakage (1) and a far-advanced stage (1). More follow-up is needed to determine the nature of the correlations between radiation dose and these results. This result concurs with the results of earlier studies (25,28,29), which reported sphincter preservation rates between 59 and 89%. Of these, one study (25) reported a higher sphincter preservation rate (89%). In this study, the total radiation dose prescribed to the tumor was 50.4 Gy. On the other hand, a lower sphincter preservation rate (59%) was found in another study (26), in which a total radiation dose prescribed was 45 Gy. The doses of 5-FU administered in the above studies ranged between 300 and 325 mg/m<sup>2</sup>/day. The results of studies (22)–(24) and the corresponding results of the present study are summarized in Table 6.

Although direct comparisons were not possible, anastomotic leakage as a major complication of rectal cancer surgery (1.8% in the present study) was no higher than in our previous study (30) on assessing the safety and the efficacy of laparoscopic colorectal surgery compared with those of conventional open surgery. In this previous study, complications in the laparoscopic surgery group were anastomotic leakage 6.5% (2/31) and bowel obstruction 6.5% (2/31). In the open group, wound infection 13.3% (4/30), urinary retention 3.3% (1/30), anastomotic leakage 3.3% (1/30) and bowel obstruction 3.3% (1/30) were found.

Total down-staging was observed in 30 (52.6%) patients in the present study. It is well known that the benefit of down-staging on local control is greatest in terms of patients who achieve pathologic complete response (31). However, the pCR was 5.3% in the present series. In three patients, complete disappearance of the primary tumor was observed in the pathology specimens. In other studies (25,28,29,32–34), reported pCRs have ranged between 0 and 33%. Grann (23) reported a pCR of 13% (9/68), whereas Janjan (28) pathologically confirmed the complete response in 27% (32/117). As compared with these results, our pCR (5.3%) was

lower. The reasons for this discrepancy are as follows. First, more Tis, T1 and T2 tumors (31%) were included in studies by Grann et al. (25) and Janjan et al. (28) comparing with the present study in which T3 tumors accounted for 96.5% of cases.

Secondly, the somewhat earlier surgery [median, 5.7 weeks post-CCRT finish (range, 4.4–8.3 weeks)] of our study comparing with that (~6 weeks) by Janjan et al. (28) might also have contributed to the lower pCR observed. A randomized trial (34) concluded that the interval between preoperative radiotherapy and surgery influences down-staging and the sphincter-sparing surgery rate in rectal cancer. In this randomized trial, rectal cancer patients were randomized before radiation therapy into two groups: a short-interval (SI) group and a long-interval (LI) group (surgery was performed within 2 weeks after completing radiation therapy in the SI group and between 6 and 8 weeks after in the LI group), and the LI group was found to show a significantly better clinical tumor response [53.1% (SI group) versus 71.7% (LI group),  $P=0.007$ ] and a pathologic down-staging rate [10.3% (SI group) versus 26% (LI group),  $P=0.005$ ]. Mehta et al. (32) undertook a prospective study to evaluate preoperative CCRT response and toxicity in T3 and T4 rectal cancer patients. Of 30 patients, 11 were stage T3N0, 14 were T3N1 and 5 were T3N1. They received 45 Gy of RT to the pelvis followed by a tumor boost (50.4–54 Gy). Surgical resection was performed 6–10 weeks post-CCRT completion, and a pCR of 33% was achieved.

In recent reports (35–37), newer agents like Irinotecan, Oxaloplatin and Xeloda (an oral 5-FU agent) have shown good responses (pCR, 31–49.3%) in locally advanced rectal cancer, and are currently being investigated as preoperative CCRT components. To evaluate the effects of these agents on tumor response, additional analysis of the clinical results of these regimens is required.

In the present study, the local recurrence rate was 5.3% (3/57), which agrees closely with those of previous reports (25,28,29), ranged from 2 to 13%. As mentioned above, our pCR (5.3%) was lower than that found by Janjan et al. (27%), who delivered 45 Gy. However, local failure in this previous study was 13%, which is higher than ours', 5.3%. In another report (25), 50.4 Gy was delivered, and pCR was obtained in 13% and local failure in 2%. Although the impact of radiation dose on pCR and local control is not known, we postulate that higher radiation doses improve both local control and pCR.

Of the three recurrences in our study, one occurred in the pre-sacral space and two occurred in the rectal stump. Although location was not found to be significantly associated with local recurrence, of the three patients that recurred, one recurred tumor was located in the upper rectum and the other two were located in the mid-rectum. Local recurrence rarely occurs in upper rectal cancer, and the case that recurred in the upper rectum (11 cm from the AV) in the present study initially had a far-advanced stage (clinical

**Table 6.** Comparison of preoperative CCRT studies for resectable rectal cancer

	Shin. (SMC) (29)	JANJAN. (MDACC) (28)	Grann. (MSKCC) (25)	Present study
No. of patients	40	117	72	57
RT dose (cGy)	4500	4500	4680 + 360	5400
Chemotherapy	FL (BI,CI), UFT (5FU, 500 mg/m <sup>2</sup> )	CI, 5-FU (5FU, 300 mg/m <sup>2</sup> )	IV, FL (5FU, 325 mg/m <sup>2</sup> )	IV, FL (5FU, 400 mg/m <sup>2</sup> )
pCR	0	27% (32/117)	13% (9/68)	5.3% (3/57)
Local failure	13% (4/33)	13% (15/117)	2% (2/72)	5.3% (3/57)
Distant failure	19% (8/37)	27% (32/117)	21%(15/72)	19.3% (11/57)
Down staging	45.5% (15/33)	62% (72/117)	56%	52.6% (30/57)
Resectability	89% (33/37)	100% (117/117)	100% (68/68)	98.2% (56/57)
Sphincter preservation	63% (20/32)	59%(59/107)	89% (31/35)	77.2% (44/57)
Toxicity (Grade 3, 4)	11% (Neutropenia)	NA	18% (Leukopenia)	3.5% (Leukopenia)
3YSR	87%	97%	95%	91.6%

pCR, pathologic complete response; 3YSR, three-year survival rate; FL, 5-fluorouracil–leucovorin; BI, bolus infusion; CI, continuous infusion; UFT, oral Uracil/Ftorafur; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

stage T3N1). Further follow up periods are needed to accurately evaluate the correlation between location and local recurrence. Moreover, these local recurrences encountered did not occur in the lower part of the rectum. Although more follow up periods are needed, our data suggest that sphincter preservation for patients with distal rectal cancer utilizing preoperative CCRT can be accomplished without compromising local control. Distant metastasis occurred in 19.3% (11/57) at the following sites: lung, 5 (45.5%); liver, 4 (36.4%); bone, 2 (18.2%); skin, 1 (9.1%); brain 1 (9.1%), and these rates concur with previous findings (Table 6).

Comparing clinical and pathologic stages, total down-staging was observed in 30 (52.6%) patients in the present study. Tumor down-staging occurred in 9 (15.8%), and N down-staging in 27 (47.4%), and both T and N down-staging occurred in 4 (7%) patients. In the present study, up-staging occurred in nine (15.8%) patients, which may have been influenced by preoperative staging inaccuracies. The accuracies of CT for assessing depth of invasion and nodal involvement have been reported to be 62.5 and 63.6%, respectively (38), whereas the accuracy of transrectal ultrasonography (TRUS) has been reported to be 67–93% for the assessment of rectal wall penetration and 62–83% for the determination of nodal status (39). Further studies (40,41) using TRUS, endorectal coil magnetic resonance imaging and positron emission tomography to stage more accurately the rectal cancer preoperatively.

Our analysis of prognostic factors for DFS and OS showed that LN involvement significantly influences DFS. However, no factor was found to significantly affect OS. Some reports (42,43), like ours', have concluded that the presence of residual tumor in lymph nodes (pathologically node positive) may predict a poor outcome. Chao et al. (44) also reported a tendency for poorer OS to be associated

with a pathologic node positive status after preoperative CCRT by univariate analysis. However, in the present study, some potential factors like circumferential margin status and DNA ploidy were not included in the analysis of clinicopathologic prognostic factors. Thus, to increase the accuracy of analysis larger scale studies are required of patients treated by curative resection after preoperative CCRT.

A Swedish rectal cancer trial (5) compared a preoperative radiation therapy plus surgery group with a surgery alone group, and found that high-dose preoperative radiation therapy reduces the rates of local recurrence and improves the survival among patients with resectable rectal cancer. In this trial, the overall 5-year survival rate was 58% in the combined group and 48% in the surgery group ( $P = 0.004$ ) (c.f. 73.3% for the present study). The results of randomized trials (4,45) that compared preoperative radiation therapy and CCRT in rectal cancer indicated that preoperative CCRT is more effective than radiation therapy in terms of reducing rates of local failure. In our study, the overall 3-year survival rate was 91.8%, and the 3-year DFS rate was 79.7%, which are in close agreement with the results of earlier studies of overall 3-year survival rates of 87–97% (28,29,46). As mentioned above, currently, concomitant RT and oxloplatin with either FU/LV or capecitabine are considered standard managements in locally advanced rectal cancer (37).

In conclusion, our findings confirm that preoperative CCRT is effective against locally advanced rectal cancer, and in accord with previous studies, 5-FU-based preoperative CCRT was found to have encouraging effects on acute toxicity, down-staging, local control and survival. In addition, anal sphincter preservation rates tended to increase and local failure rates tended to decrease at a moderately higher radiation dose compared with previous reports.



**Conflict of interest statement**

None declared.

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