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ORIGINAL ARTICLE

Preoperative chemoradiotherapy improves local recurrence free survival in locally advanced rectal cancer

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Summary

Purpose: *Preoperative chemoradiotherapy (pre-CRT) followed by total mesorectal excision (TME) is the recommended therapy for patients with locally advanced rectal cancer (LARC). The primary aim of this study was to compare the rates of local and distant recurrence and overall survival (OS) in LARC patients who received pre-CRT vs postoperative (post) CRT.*

Methods: *The medical records of 158 rectal cancer patients with clinical stage T3, T4 or N positive disease who received either pre-CRT or post-CRT between 2000-2009 were retrospectively analysed. Pre-CRT employed protracted 5-fluorouracil (5FU) infusion, whereas post-CRT included bolus 5FU and leucovorin concurrently with radiation therapy (RT). Radiation dose was 50.4 Gy in 82% and 45 Gy in 18% of the patients.*

Results: *158 patients (65 females, 93 males) were analysed. Median age was 56.5 years (range 19–78). Fifty-three (34%) patients received pre-CRT and 105 (66%) post-CRT. Median follow-up was 43.3 months (range 8-182) and 47.6 months (range 9-194) in pre-CRT and post-CRT patients, respectively. After pre-CRT, significant downstaging was achieved. However, the type of surgical resection was not influenced by the administration of pre-CRT in tumors ≤5 cm distant from the anal verge (p=0.3). Pathologic complete response was achieved in 20% of the patients in the pre-CRT group. Local recurrence free survival (LRFS) at 5-years was 89.2% in the pre-CRT and 74.8% in the post-CRT group (p=0.04). Distant recurrence free survival (DRFS) at 5-years was 81.7% and 68.5 % in pre-CRT and post-CRT groups, respectively (p=0.1). OS was similar in the two groups (71.4 vs 64.4%, p=0.9).*

Conclusion: *Treatment of LARC with pre-CRT followed by surgery improved LRFS as compared to surgery followed by post-CRT, but failed to improve DRFS or OS in our patient population.*

Key words: *locally advanced, postoperative chemoradiotherapy, preoperative chemoradiotherapy, rectal cancer, treatment outcome*

Introduction

LARC has high local recurrence risk due to the absence of surrounding serosa. Technical difficulties in obtaining wide surgical margins at resection also increase the risk for recurrence. Therefore, treatment of LARC should include pre-CRT or post-CRT. Fluoropyrimidine-based chemotherapy is recommended concurrently with RT. The German Rectal Cancer Study Group compared pre- vs post-CRT in the treatment of clinical stage II/III rectal cancer. The results of this study indicated that pre-CRT was associated with significant reduction in local recurrence and treatment-associated toxicity; however, there was no difference in OS [1]. One possible drawback of pre-CRT is overtreatment of early lesions which would not require adjuvant therapy [1,2]. Tumors in the up-

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per and middle rectum can usually be managed with low anterior resection (LAR), coloanal anastomosis and preservation of the anal sphincter. Tumors in the distal rectum may need abdominoperineal resection (APR) which obligates permanent colostomy with high rate of surgical complications. Mesorectum is a potential metastatic site for rectal cancer. TME has become the standard of care in rectal cancer surgery because it results in significantly reduced local recurrence rate (LRR) [3-5].

In this study we aimed to retrospectively evaluate local and distant recurrence rates and OS in patients undergoing pre-CRT and post-CRT in LARC. Acute and late complications and treatment toxicity were also evaluated.

Methods

Patients

The medical records of patients with clinical stage T3-T4N0 or N1 rectal cancer who received either pre-CRT or post-CRT between 2000-2009 were retrospectively analysed. Patients with histological diagnosis of rectal adenocarcinoma were included in the study provided that the tumor was located in the distal 15 cm from the anal verge. Preoperative staging was performed with thoracic and abdominal computed tomography (CT) or abdominal and pelvic magnetic resonance imaging (MRI). Endoscopic ultrasound was optional. Patients were not included in the study if they had metastatic disease, positive surgical margins, incomplete CRT, poor performance status (Eastern Cooperative Oncology Group/ ECOG >2), inadequate renal and hepatic function, or other second primary cancers. Patients who did not undergo surgery for various reasons were excluded.

Treatment

The chemotherapeutic regimen used concurrently with preoperative RT was protracted 5FU infusion (225 mg/m^2/day for 28 consecutive days). Four cycles of adjuvant bolus 5FU (425 mg/m^2/day) and leucovorin (20 mg/m^2/day) (Mayo regimen) on days 1-5 every 28 days were administered to these patients after surgery, as indicated.

Bolus 5FU and leucovorin was employed on days 1-4 every 28 days concurrently with postoperative RT in the 3rd and 4th cycles of the planned 6 cycles of adjuvant chemotherapy. Eighty-two percent of the patients received 50.4 Gy and 18% received 45 Gy RT in 5 weeks. Surgical resection was performed 52 days (median) after completion of pre-CRT. APR or sphincter-saving surgery was performed, as indicated. TME was not mandatory and was employed at the discretion of the operating surgeon.

Follow-up

Patients were followed every 3 months for 2 years and every 6 months between 3-5 years and annually thereafter. Evaluation included clinical examination, complete blood count, serum biochemistry, serum carcinoembryonic antigen (CEA) level, thoracic and abdominal CT and colonoscopy as indicated. Adverse events were defined using to WHO criteria. Recurrence was diagnosed on the basis of clinicoimaging findings and/or elevated CEA levels. Pathologic confirmation was obtained in selected cases.

Statistics

Patient characteristics, type of surgery, time to surgery after completion of pre-CRT, distance of tumor from the anal verge, clinical/pathological (c) T and N stages, presence of pathological complete response (pCR), time to adjuvant treatment after completion of surgery, disease recurrence (local or distant), acute and late toxic effects, surgical complications and deaths due to any cause were registered. Categorical and continuous variables were compared with chi-square and Mann-Whitney U tests, respectively. LRFS and DRFS were defined as the time from diagnosis to the detection of any local or distant recurrence, respectively. OS was defined from the time of diagnosis to death from any cause. LRFS, DRFS and OS were estimated by using the Kaplan-Meier method. Log-rank test was used to evaluate differences between groups. The Cox proportional-hazards model was used to calculate hazard ratio and 95 percent confidence intervals (95% CI).

Results

Patients

A total of 158 patients (65 females, 93 males) were registered and analysed. Median age was 56.5 years (range 19–78). Fifty-three (34%) patients received pre-CRT and 105 (66%) post-CRT. Median follow-up was 45.5 months (range 7.6–197). Patient characteristics are summarized in Table 1. Pre-CRT group had more cT4 and node positive disease. Median distance of tumor from the anal verge was 8 cm (range 0-15). Overall, 35% of tumors were within ≤5 cm distance from the anal verge (pre-CRT group 50%, post-CRT group 28%). Preoperative CRT did not have any impact on the final surgery type in tumors ≤5 cm distant from the anal verge (p=0.3).

Efficacy of preoperative CRT

After pre-CRT, significant downstaging was achieved in clinical stage (Table 2). Downstaging rates were 33% and 73% according to T stage and

Table 1. Patient clinical characteristics

Characteristics	*Pre-CRT N=53 N (%)*	*Post-CRT N=105 N (%)*	*p-value*
Age, years, median (range)	55 (26-77)	58 (20-78)	0.2
Sex			0.1
Male	36 (68)	57 (54)	
Female	17 (32)	48 (46)	
Clinical T stage			
cT3	42 (79)	84 (80)	0.6
cT4	9 (17)	5 (5)	0.02
Unknown	2 (4)	16 (15)	0.01
Clinical N stage			0.01
cN positive	26 (49)	27 (26)	
cN negative	26 (49)	62 (60)	
Unknown	1 (2)	16 (14)	
Type of surgery			0.18
LAR	32 (60)	77 (73)	
APR	20 (38)	28 (27)	
Unknown	1 (2)		
Tumor location (cm)			0.015
<5	25 (47)	29 (27)	
5-10	22 (41)	40 (38)	
>10	4 (8)	22 (20)	
Unknown	2 (4)	14 (15)	

LAR: low anterior resection, APR: abdominoperineal resection

Table 2. Downstaging with preoperative chemoradiation

	Pathological stage					
Clinical stage (N)	*pT0*	*pT2*	*pT3*	*pT4*	*Node +*	*Downstaging (%)*
T3 (42)	9	4	27	2		31
T4 (9)	1	1	2	5		44
Unknown (2)	0	0	2	0		
Total						33
Lymph node metastasis (26)					19	73

Table 3. Downstaging with preoperative chemoradiation

Histopathological characteristics	*Pre-CRT N (%)*	*Post-CRT N (%)*	*p-value*
Histopathological findings			
pT2	5 (8)	10 (9.5)	0.2
pT3	31 (60)	86 (82)	0.01
pT4	7 (12)	9 (8.5)	0.6
pCR	10 (20)	NA	NA
pN+	19 (36)	67 (64)	0.01
Number of lymph nodes harvested			0.028
Median	10	13	
Range	3-27	1-40	
Mucinous component >50%	9 (20.4)	9 (9.1)	0.05
Lymphatic invasion	22 (47.8)	62 (74.7)	0.004
Vascular invasion	13 (27.7)	26 (29.5)	0.84
Perineural invasion	19 (35)	32 (30)	0.8
Poor differentiation	4 (7.5)	3 (3)	0.1

NA: not available

Table 4. Grade 3/4 acute toxicities of chemoradiation

Grade 3-4 toxicity	*Pre-CRT N (%)*	*Post-CRT N (%)*	*p- value*
Hematologic	2 (4)	9 (8.5)	0.032
Diarrhea	2 (4)	7 (6.5)	0.04
Nausea & vomiting	1 (2)	4 (3)	0.08
Mucositis & dermatitis	8 (15)	12 (11)	0.09
Other	3 (6)	12 (11)	0.01
Total	9 (17)	26 (34)	0.04

Table 5. Long-term surgical complications

Complications	*Pre-CRT N (%)*	*Post-CRT N (%)*	*p-value*
Anastomotic site stenosis	1 (2)	5 (4)	0.045
Anastomosis leakage	1 (2)	2 (2)	0.5
Pelvic abscess	3 (6)	3 (3)	0.04
Fistula formation	0	4 (4)	0.02
Herniation	0	5 (5)	0.01
Total	5 (10)	19 (18)	0.03

N stage, respectively. Pathologic CR was achieved in 10 patients (20%) in the pre-CRT group. Detailed histopathological characteristics are summarized in Table 3. Patients of the pre-CRT arm had lower number of lymph nodes harvested (p=0.028) associated with lower incidence of lymphatic invasion (p=0.004) and lymph node metastasis (p=0.01).

Toxicity of CRT and surgery

Overall grade 3/4 acute toxicities of pre-CRT and post-CRT were 17 and 34%, respectively (p=0.04). Surgical complications of pre-CRT and post-CRT were 10% and 18%, respectively (p=0.03). Details of acute CRT and long-term surgical complications are depicted in Tables 4 and 5.

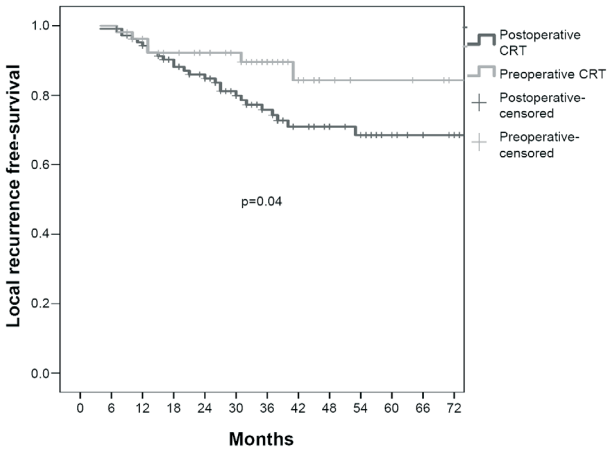

Figure 1. Local recurrence free survival in patients with preoperative chemoradiation vs postoperative chemoradiation.

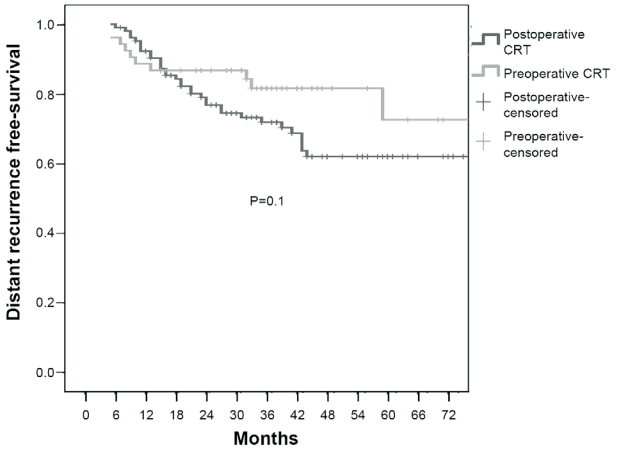

Figure 2. Distant recurrence free survival in patients with preoperative chemoradiation vs postoperative chemoradiation.

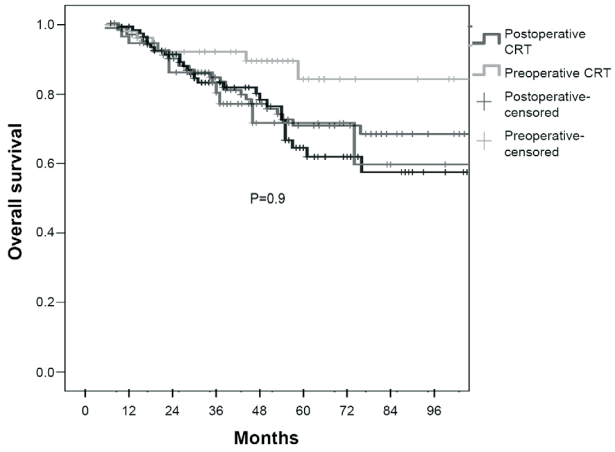

Figure 3. Overall survival in patients with preoperative chemoradiation vs postoperative chemoradiation.

Survival

Median follow-up time of patients who underwent pre-CRT and post-CRT were 43.3 months (range 8-182) and 47.6 months (range 9-194), respectively. LRFS at 5-years was 89.2% in the pre-CRT and 74.8% in the post-CRT groups (p=0.04). Six pre-CRT patients and 29 post-CRT patients had local recurrence as the first event (Figure 1). The incidence of distant recurrence was not different in the pre-CRT and post-CRT groups. DRFS at 5-years was 81.7% in the pre-CRT and 68.5% in the post-CRT groups (p=0.1). Ten pre-CRT patients and 34 post-CRT patients had a distant recurrence as the first event (Figure 2). Thirteen patients in pre-CRT and post-CRT groups had a concurrent distant and local recurrence as a first event. In both treatment arms, liver was the most common first metastatic site.

Twelve pre-CRT patients and 38 post-CRT patients died during follow-up (Figure 3). OS rate was similar in the pre-CRT and post-CRT patients. Five-year OS rates were 71.4% in the pre-CRT patients vs 64.4% in the post-CRT patients (p=0.9).

Discussion

Patients with LARC have a higher incidence of local recurrence with surgery alone. Several studies confirmed the efficacy of shorter course of RT (25 Gy over 5 days) for the treatment of rectal cancer [6-8]. The Swedish Rectal Cancer Trial showed survival advantage and decreased LRR in patients receiving short-course preoperative RT [6]. Other studies [7,8] only showed a decreased rate of LRR, but no survival advantage. However, short-course preoperative RT increased postoperative complications [6]. Several randomized studies showed effectiveness of CRT compared to RT alone [9,10]. The EORTC 22921 trial showed that compared to RT alone, pre-CRT was associated with significantly higher pCR, lower pN stage, and less frequent lymphatic, venous and perineural invasion [10]. However, this trial showed no significant effect on survival despite the significantly lower LRR [10,11]. The FFCD 9203 trial, comparing preoperative RT with CRT showed higher grade 3/4 acute toxicity and pCR rates with CRT [12]. There was no difference in sphincter preservation rates. Although LRR was lower in the pre-CRT group, OS was similar [12]. In a metaanalysis of 4 studies, pre-CRT was shown to enhance pCR and decrease LRR in stage II/III rectal cancer compared to preoperative RT alone with no advantage in

disease-free survival (DFS) or OS. Moreover, pre-CRT increased acute toxicity [9].

A large prospective randomized trial from The German Rectal Cancer Study Group compared pre-CRT vs post-CRT in 823 patients with clinical T3, T4 or N positive rectal cancer [1]. All patients underwent TME. This study showed that pre-CRT was associated with significantly decreased 5-year cumulative incidence of LRR (6 vs 13%; p=0.006) and treatment associated toxicity (27 vs 40%; p=0.001) with a 46-month median follow-up. However, the pre-CRT arm did not show 5-year OS advantage (76 vs 74%; p=0.8). Moreover, complete resection and sphincter-sparing surgery rates were also similar in the two treatment arms. Interestingly, among 194 patients with low-lying tumors who were preoperatively anticipated to require APR, a statistically significant increase in sphincter preservation was achieved among patients who received pre-CRT (39 vs 19%; p=0.004).

A second prospective randomized trial from NSABP (R-03) comparing pre-CRT vs post-CRT in 267 LARC patients showed 15% pCR rate after pre-CRT [13]. The pre-CRT arm was associated with a significantly higher rate of 5-year DFS (64.7 vs 53.4%; p=0.011) and a trend of better OS (74.5 vs 65.6%; p=0.065); yet, LRR was not different between the two treatment arms (10.7% in both groups). There was no increase in sphincter preservation rates with pre-CRT. LRR was high in the NSABP R-03 trial compared to the German trial, possibly because of low TME rates.

Kao and colleagues compared pre-CRT vs post-CRT in 136 patients with T3, T4 and N positive disease [14]. All patients underwent TME. pCR rate following pre-CRT was 24.6%. Moreover, pre-CRT was associated with significantly decreased 5-year LRR (5.8 vs 19.4%; p=0.02) and increased OS (88.4 vs 65.7%; p=0.001). However, the incidence of distant metastases was similar in both treatment arms (26.1 vs 40.3%; p=0.11). Although patients undergoing pre-CRT had a significantly higher sphincter preservation rate, there was no difference in the preserved anorectal function at 5-year follow-up.

In our study, pre- CRT was associated with significantly decreased 5-year LRR. LRFS at 5 years was 89.2% in the pre-CRT compared to 74.8% in the post-CRT group (p=0.04), but LRR was high in our series compared to the German study, probably because of low rates of TME. Moreover, preoperative clinical T4 stage was higher in our series compared to the German study. The incidence of distant recurrence was not different between pre-CRT and post-CRT patients in our study. DRFS at 5 years was 81.7% in the pre-CRT and 68.5% in the post-CRT groups (p=0.1), similar to the literature data [1,11,12]. Five-year OS rates were 71.4% in the pre-CRT vs 64.4% in the post-CRT group (p=0.9), similar to prior studies [1,11,12]. The type of surgical resection was not affected by the administration of pre-CRT in tumors ≤5 cm distant from the anal verge (p=0.3). However, we were not able to determine the percentage of patients who could achieve sphincter preservation after pre-CRT in comparison to patients who were deemed to require APR in their preoperative assessment. Finally, along the lines of previous studies [1,13,15,16], acute and late toxicities were encountered more frequently in post-CRT patients in our series.

In conclusion, treatment of LARC with pre-CRT followed by surgery as compared with surgery followed by post-CRT, improved LRFS, but did not improve DRFS or OS in our patient cohort. Pre-CRT was more tolerable with less acute and late toxicities.

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