

## RESEARCH ARTICLE

# Long Term Outcomes of Preoperative *versus* Postoperative Concurrent Chemoradiation for Locally Advanced Rectal Cancer: Experience from Ramathibodi Medical School in Thailand

Pichayada Darunikorn<sup>1</sup>, Putipun Puataweepong<sup>1\*</sup>, Mantana Dhanachai<sup>1</sup>, Somjai Dangprasert<sup>1</sup>, Thiti Swangsilpa<sup>1</sup>, Chomporn Sitathanee<sup>1</sup>, Chuleeporn Jiarpinitnun<sup>1</sup>, Poompis Pattaranutaporn<sup>1</sup>, Keerantikan Boonyawan<sup>1</sup>, Pichai Chansriwong<sup>2</sup>

### Abstract

**Objectives:** The study analyzed and compared the long term outcome in locally advanced rectal cancer treated with preoperative and postoperative concurrent chemoradiation (CCRT). **Materials and Methods:** A retrospective review of 105 patients with stage T3-T4 or regional lymph node positive adenocarcinoma of rectum treated with preoperative or postoperative CCRT at Ramathibodi Hospital during 2005 to 2010 was performed. The results of treatment were reported with 5-year overall survival (OS), 5-year locoregional recurrence free survival (LRFS), and toxicity according to preoperative versus postoperative concurrent chemoradiation (CCRT) groups. **Results:** Among 105 patients, 34 (32%) were treated with preoperative CCRT and 71 (68%) with postoperative CCRT. At the median follow-up time of 50.5 months (range 2-114 months), five-year OS and LRFS of all patients were 87% and 91.6%, respectively. The study found no difference in 5-year OS (81.7% vs 89.2%) or LRFS (83.4% vs 95.1%) between preoperative versus postoperative CCRT. Seven cases of loco-regional recurrence were diagnosed, 4 (11.8%) after preoperative CCRT and 3 (4.2%) after postoperative CCRT. The recurrent sites were anastomosis in all patients. There was no significant factor associated with outcome after univariate and multivariate testing. Grade 3 or 4 acute and late complications were low in both preoperative and postoperative CCRT groups. **Conclusions:** Locally advanced rectum cancer patients experience good results with surgery and adjuvant concurrent chemoradiation.

**Keywords:** Rectal cancer - chemoradiation - locally advanced - outcome

*Asian Pac J Cancer Prev*, 16 (16), 7315-7319

### Introduction

Rectal cancer is the fifth most common cancer in Thailand. The annual incidence per 100,000 is 1935 in male and 1477 in female (Moore et al., 2010). The standard treatment for locally advanced rectal cancer (T3-T4 or N positive staging) is transabdominal surgery with adjuvant concurrent chemoradiation (CCRT). Several studies have consistently shown the benefit and better outcome of adjuvant CCRT in term of local control (LC), disease free survival (DFS) and overall survival (OS) than adjuvant radiation or chemotherapy alone (Thomas and Lindblad, 1988; Krook et al., 1991; Wolmark et al., 2000; Sauer et al., 2004; Kacaret et al., 2009) With regard to adjuvant CCRT for locally advanced rectum cancer, there are two treatment options consisting of preoperative CCRT

and postoperative CCRT. Although both preoperative and postoperative CCRT can be effective, preoperative treatment has emerged as the standard of care, because it is associated with tumor downstaging, improved resectability and potential for expanded sphincter preservation options in the distal rectum and lower complication when compared to postoperative setting. However, there is no difference in the overall survival rate between preoperative and postoperative CCRT (Sauer et al., 2004). Although the outcome of rectum cancer treated with surgery and adjuvant chemoradiation is currently published worldwide, most of the reports are from the western countries, and there are relatively few studies from Asian countries (Yeh et al., 2012; Lee et al., 2013; Akhavan et al., 2014; Park, 2014). The primary objective of this study is to analyze the difference of long term treatment outcomes

<sup>1</sup>Radiation and Oncology Unit, Department of Radiology, <sup>2</sup>Medical Oncology Unit, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand \*For correspondence: putipun.pua@mahidol.ac.th

between preoperative CCRT versus postoperative CCRT for locally advanced rectal cancer treated in our institute.

### Materials and Methods

This study was approved by our institution review board. Informed consent was obtained from all patients. Inclusion criteria were: 1) patients who had pathological confirmed of adenocarcinoma of rectum, 2) clinical or pathological stage T3, T4 or regional lymph node positive, and 3) patients received either preoperative CCRT or postoperative CCRT at Ramathibodi Hospital.

Both preoperative and postoperative CCRT groups were given with combined modality treatment of both 5-FU based chemotherapy and radiotherapy to the whole pelvis. The patients in the preoperative CCRT group initially received radiation and chemotherapy followed by surgery 4-6 weeks after completion of CCRT; then adjuvant chemotherapy was administered thereafter to complete the regimen. In the postoperative CCRT group, adjuvant CCRT was delivered 4-6 weeks after surgery. Adjuvant radiation therapy was delivered to the whole pelvis through anterior and posterior parallel-opposed field (AP/PA), three-field or four-field box technique with 2 or 3-dimensional treatment planning. The common radiation dose was 45 -50 Gy (1.8-2 Gy/fraction with or without 5.4 Gy additional tumor bed boost. Linear accelerator with megavoltage 6 or 10 MV X-ray was used. The curative surgery methods of either low anterior resection (LAR) or abdominoperineal resection (APR) were decided by individual surgeon.

After completion of the treatment, all patients were under surveillance by the radiation oncologist, medical oncologist and surgeon. The surveillance program could vary from patient to patient depending on the preference of each physician. The history and physical examination were performed for every visit. Carcinoembryonic antigen (CEA) was done at 4-6 weeks after surgery, and then every 3-6 months thereafter. Colonoscopy was scheduled at the first and 4th -5th years after surgery. Other investigations such as CT or MRI scan were performed when persistent or recurrent tumor was suspected. Acute complications (within 6 months after finishing radiotherapy) were recorded and graded according to criteria of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Late complications (6 month after radiotherapy) were recorded and graded according to the late toxicity criteria of the LENT SOMA system.

#### Statistical analyses

Primary endpoints were loco-regional recurrence free survival (LRFS) and overall survival (OS). The factors that impact on the LRFS and the complication from treatment were also secondary endpoints. OS was the time from surgery to death from any cause. LRFS was the time from surgery to recurrence at anastomotic site, surgical stump, perineal scar, regional lymph node or death whichever came first or the most recent follow up.

Statistical analyses were performed using Statistical Package for Social Sciences for Windows version 18.0 (SPSS V.18.0; SPSS Inc., Chicago, IL., USA).

Survival times were calculated using Kaplan-Meier method. Univariate analysis was evaluated by log-rank test. Multivariate analysis was performed using Cox proportional hazard regression model to explore factors that might associate with the outcome of treatment. A p-value of < 0.05 was considered to indicate statistically significant difference.

### Results

During January 2005 to December 2010, 186 patients were included in the study. Eighty-one patients were excluded due to no pathological data (28 patients), no surgical data (13 patients), two primary cancer (9 patients) and refused radiation treatment (31 patients). Therefore, 105 patients were eligible for analysis. The median follow-up time was 50.5 months (ranging from 2 to 114 months). Twelve patients (11.4%) were loss to follow-up.

#### Patients and treatment characteristics

Of the 105 patients included in this study, 34 patients (32%) received preoperative CCRT, whereas 71 patients (68%) were treated with postoperative CCRT. The baseline characteristics were quite similar between the preoperative CCRT and the postoperative CCRT groups except for imbalances tending towards higher proportions of low lying tumor (tumor located < 5 cm from anal verge) in the preoperative CCRT group (52.9%) versus 12.7% in the postoperative CCRT group.

The median follow-up time for all 105 patients was 50.5 months (range, 2 -114 months), which was longer in postoperative CCRT group (52.4 month; range, 2-114 months) than preoperative CCRT group ( 46.5 month; range, 2-89 months). Twelve patients (11.4%) (4 in preoperative group versus 8 in postoperative group) were lost to follow-up.

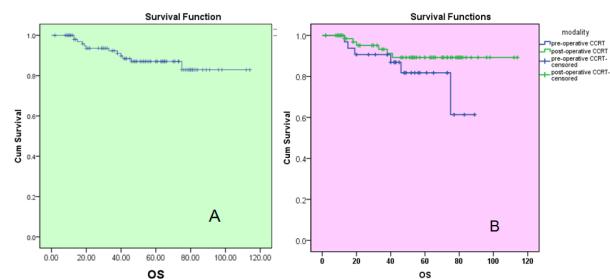


Figure 1. A. Overall Survival (OS) of All Patients and B. OS in Preoperative and Postoperative CCRT Group

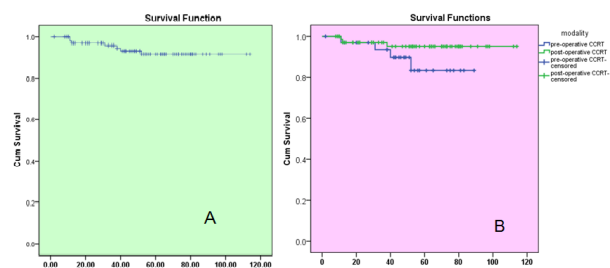


Figure 2. A. Locoregional Recurrence free Survival (LRFS) of All Patients and B. LRFS in Preoperative and Postoperative CCRT Group

**Table 1. Patient and treatment characteristics**

Parameters	Pre-op CCRT (n=34)	Post-op CCRT (n=71)
Gender		
Male	20	44
Female	14	27
Age (years)	Mean = 59.8	Mean = 59.9
≤50	7 (20.59%)	13(18.31%)
>50	27(79.41%)	58(81.69%)
ECOG		
0-1	18(52.94%)	45(63.38%)
>1	16(47.06%)	26(36.62%)
T staging	clinical	pathological
T1	0	0
T2	0	6(8.45%)
T3	29(85.29%)	32 (94.1 %)
T4	5(14.71%)	2 (5.9%)
N staging		
N 0	8(23.53%)	7(20.6%)
N 1	19(55.88%)	20(58.8%)
N 2	7(20.59%)	7(20.6%)
TNM staging		
Stage II	7(20.59%)	7(20.6%)
Stage III	27(79.41%)	7(20.6%)
Pathological grading		
Well differentiated	20(58.82%)	37(52.11%)
Moderate differentiated	10(29.41%)	27(38.03%)
Poorly differentiated	2(5.88%)	5(7.04%)
Not specified	2(5.88%)	2(2.82%)
Distance from AV		
< 5 cm	18(52.94%)	9(12.68%)
5-10 cm	10(29.41%)	35(49.30%)
>10 cm	5(14.71%)	25(35.21%)
Unknown	1(2.94%)	2(2.82%)
Surgery		
LAR	15(44.12%)	46(64.79%)
APR	16(47.06%)	18(25.35%)
Other	3(8.82%)	7(9.86%)
Chemotherapy regimen		
Fluorouracil	7(20.59%)	10(14.08%)
Fluorouracil/Leucovorin	24(70.59%)	54(76.06%)
Capecitabine	2(5.88%)	4(5.63%)
Unknown	1(2.94%)	3(4.23%)
Radiation technique		
2 Dimensional	13(38.24%)	47(66.20%)
3 Dimensional	21(61.76%)	24(33.80%)
Machine		
Cobalt-60	0	0
Linac 6 MV	2(5.88%)	8(11.27%)
Linac 10 MV	32(94.12%)	63(88.73%)
Radiation dose		
< 45 Gy	1(2.94%)	5(7.04%)
45-50.4 Gy	24(70.59%)	49(69.01%)
≥ 50.4 Gy	8(23.53%)	17(23.94%)

LAR= Low anterior resection, APR=Abdominoperineal resection , Gy= Gray

Patient and treatment characteristics which were categorized by preoperative and postoperative CCRT are summarized in Table 1.

#### Overall survival (OS)

At the last follow up, 93 of patients (88.6 %) were alive, but 12 patients (11.4%) died. The 5-year OS rate was 87.0% (Figure 1A). The 5-year OS rate was 81.7% in the preoperative CCRT group versus 89.2 % in the

postoperative CCRT group (Figure 1B).

#### Locoregional recurrent free survival (LRFS)

At the last follow up, 86 patients were free of disease and 17 patients were alive with disease (7 patients with loco-regional disease and 4 patients with both loco-regional and distant disease).The 5-year LRFS rate was 91.6 % for all patients (Figure 2A). For the preoperative CCRT group, the 5-year LRFS rate was 83.4 % versus

95.1 % in the postoperative CCRT group (Figure 2B). There was no factor associated with LRFS after univariate testing.

### Complications of the treatment

Twenty patients had acute grade 3 or 4 toxicity, most of which was diarrhea for 18 patients (17.1%). Eight (7.6%) and 1 (0.95%) patients developed late gastrointestinal (GI) and genitourinary (GU) toxicity, respectively.

There were 6 (17.65%) and 14 (19.72) patients with acute grade 3 or 4 toxicity in the pre-operative and the postoperative CCRT group, respectively. Only 4(12.9%) and 7 (9.9 %) developed late grade 3 or 4 toxicity in the preoperative and the postoperative CCRT group, respectively.

## Discussion

Trans-abdominal surgery with sphincter preservation surgery (low anterior resection) and non-sphincter preservation surgery (abdominoperineal resection) is the standard treatment of locally advanced rectum cancer. However, after surgery alone, the unacceptably high local recurrence has led to several studies exploring the potential benefit of adjuvant treatment with chemotherapy and radiation. Many studies have confirmed the superior outcome of adjuvant concurrent chemoradiation in term of improved overall survival, disease free survival and local control than surgery alone, adjuvant chemotherapy alone or adjuvant radiotherapy alone. (Thomas & Lindblad, 1988; Krook et al., 1991; Wolmark et al., 2000; Miller et al., 2002) Regarding adjuvant radiation (RT) for locally advanced rectum cancer, there are two treatment options consisting of preoperative CCRT and postoperative CCRT. Preoperative and postoperative RT have some different advantages and disadvantages. The advantages of postoperative RT is the ability to selectively treat patients at high risk of local recurrence on the basis of true pathologic staging. Disadvantages include a potentially hypoxic postsurgical bed, making radiation and chemotherapy less effective, and potentially higher complications because of increased small bowel in the radiation field and required larger radiation volumes, particularly in patients undergoing APR, where the perineal scar may need to be covered. In contrasting to preoperative RT, the benefits such as tumor downstaging, improved resectability, and possibility for sphincter preservation options in the distal rectum are mentioned. The main disadvantage of the preoperative radiation is the possible overtreatment of the early stage tumors due to unavailable pathological staging. Nowadays, in the United States, preoperative CCRT has become widely accepted, but in other parts of the world, especially in the developing countries such as Thailand, the use of preoperative CCRT might be limited due to the difference in patient characteristics, the preference of physicians and the limited resource such as preoperative MRI or transrectal ultrasound. In addition, the majority of the studies regarding the outcomes of locally advanced rectum cancer were from the western countries, and there are still a relatively few reports from Asian countries. Our study was therefore to analyze the outcome of preoperative

versus postoperative CCRT in locally advanced rectum cancer in Ramathibodi Hospital, Thailand.

More recently, multiple phase III randomized controlled trials comparing preoperative and postoperative CCRT in locally advanced rectal cancer consistently reported the superior outcome of preoperative CCRT than postoperative CCRT (Sauer et al., 2004; Roh et al., 2009; Park et al., 2011). For the example, NSABP R-03 trial showed significant better 5-year disease free survival (DFS) in preoperative CCRT (64.7 %) as compared with postoperative CCRT group (53.4 %). (Roh et al., 2009) The German rectal cancer group, however, did not present 5-year DFS benefit but confirmed significant differences in locoregional recurrence rates between preoperative (6%) versus postoperative groups (13%) ( $p = 0.006$ ) with associated toxicity reduction in both acute and long term toxic effects (Sauer et al., 2004). Nevertheless, the benefit of preoperative CCRT did not translate to improve overall survival compare to postoperative CCRT.

Although, preoperative CCRT is acceptable nowadays, most of patients (68 %) in this study were treated with postoperative CCRT. This was probably because the data in this study came from the older era that the lack of level I evidence supported the use of preoperative CCRT rather than postoperative CCRT, and advanced imaging for preoperative staging such as MRI and transrectal ultrasound was not available. Nevertheless, after reviewing the practice of locally advanced rectal cancer from 2005 to 2010 in our hospital, there was a tendency to increase preoperative CCRT treatment in the new era.

For all patients, our study showed 5yr-OS and 5yr-LRFS of 87 % and 91.6 %, respectively. These results are similar to those of the other studies, in which the overall survival rates were in the range of 56-80% and the disease free survival rates were of 58-68% (Thomas & Lindblad, 1988; Arnaud et al., 1997; Kacar et al., 2009; Rodel et al., 2012; Sauer et al., 2012). With respect to our results, for the preoperative CCRT group, 5 year OS and LRFS were 81.7%, and 83.4 %, respectively, and for the postoperative CCRT group, 89.2% and 95.1%, respectively without statistically significant difference. The outcomes of the post-operative CCRT group appeared to be better than pre-operative CCRT group that contrast to other aforementioned studies (Sauer et al., 2004; Roh et al., 2009). This contradictory results of our study due to a retrospective nature, the relatively small number of patients in preoperative group, not routinely performing CT/MRI imaging or colonoscope for follow up evaluation. According to the higher 5yr-LRFS in post-operative group, we explored the patients and treatment characteristics of all 7 loco-regional relapse patients which affected the result. However, there was no difference in both groups.

In our study, however, there were some limitations including a retrospective nature, the relatively small number of patients in the preoperative group, incomplete medical records, and not routinely performing CT/MRI imaging or colonoscope for follow up evaluation. Nevertheless, the results of our study did provide important data which help support our routine practices and further adjust and improve the treatment for patients with locally advanced rectum cancer.

In conclusion, the study has demonstrated good LRC, OS, DFS and low complication with multimodalities approach in locally advanced rectum cancer treated in Ramathibodi Hospital.

## Acknowledgements

The authors would like to thank all the staff contributing to the patients' care, Ms. Umaporn Udomsubpayakul, Medical Statistics Unit, Ramathibodi Hospital for contribution statistic program management and Professor Amnuay Thithaphandha helped edit the English language.

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