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Original Article

Retrospective Study on the Effect of Preoperative Versus Postoperative Chemoradiation for Rectal Carcinoma

Siripong Sirikurnpiboon*
Supakade Surabenjawong*
Viroj Laosunthornsiri†
Burin Awapittaya*

**Department of Surgery, Rajavithi Hospital, Bangkok, Thailand*
†Department of Surgery, National Cancer Institute, Bangkok, Thailand

Abstract

Background: In the present, there are two types of giving radiotherapy together with chemotherapy for treatment of rectal carcinoma: neoadjuvant chemoradiation (CRT) and adjuvant CRT. A study conducted overseas has found that patients given neoadjuvant CRT had better disease-free survival rate than patients given adjuvant CRT, with no difference in overall survival rate and distant metastasis rate. However, there is no study comparing the efficacy of neoadjuvant CRT and to adjuvant CRT in Thai patients.

Materials & Methods: In this retrospective study, patients were divided into two groups: the group which received neoadjuvant CRT (54 patients) and the group receiving adjuvant CRT (71 patients). The objective of this study was to determine disease-free survival rate and overall survival rate of the treatment comparing neoadjuvant and adjuvant CRT. Lastly, the correlation between the status of K-ras gene and outcome of the treatment was analyzed.

Results: The group with neoadjuvant CRT had disease-free survival rate as follows: 1 year at 94.2%; 2 years at 81.8%; 3 years at 70.4%; and 5 years at 70.4% compared with the group with adjuvant CRT who had disease-free survival rate as follows: 1 year at 82.4%; 2 years at 73.5%; 3 years at 57.1%; and 5 years at 46.1%. The group which received neoadjuvant CRT had statistically significant better disease-free survival rate than the group receiving adjuvant CRT (P=0.034). The group which received neoadjuvant CRT had overall survival rate: 1 year at 96.2%; 2 years at 90.1%; 3 years at 82.1%; and 5 years at 64.5% compared with the adjuvant chemoradiation group which had overall survival rate: 1 year at 89.7%; 2 years at 85.3%; 3 years at 69.9%; and 5 years at 55.4%. It was found that the group receiving neoadjuvant CRT did not have statistically significant better overall survival rate than the adjuvant CRT group (P=0.147).

Conclusions: Patients who received neoadjuvant CRT had better outcome in term of disease-free survival than those with adjuvant CRT.

Correspondence address : *Siripong Sirikurnpiboon; Department of Surgery, Rajavithi Hospital, 2 Phayathai Road, Rajthevee, Bangkok 10400, Thailand; Tel/Fax: +66 2354 8080; Email: general.surgery.rajavithi@gmail.com*

Introduction

The treatment of rectal carcinoma which has poached through muscularis propria (T3) or spread into lymph metastasis (N1) by surgery only is not enough. Radiotherapy and chemotherapy treatments have to be made together with an operation. There are two types of giving radiotherapy together with chemoradiation (CRT): neoadjuvant CRT and adjuvant CRT. Previous studies had shown that neoadjuvant CRT had better disease-free survival rate than adjuvant CRT with no difference between overall survival rate and distant metastasis rate[1,2]. However, there has been no study on the efficiency of neoadjuvant CRT in Thai patients in comparison to adjuvant CRT. Therefore, this study aimed to evaluate the efficacy of neoadjuvant CRT compared with adjuvant CRT in Thai patients with stage II and III rectal carcinoma.

Patients and Methods

This was a retrospective study in patients with rectal carcinoma who had been treated by radiotherapy at the National Cancer Institute during 1990-2009. The patients might also be operated or given chemotherapy at other hospitals. The inclusion criteria and exclusion criteria are shown in Table 1.

The sample was divided into 2 groups: the patient group receiving neoadjuvant CRT (54 patients) and the group receiving adjuvant CRT (71 patients). The researchers obtained data of the sample groups from the patients' medical records and from telephoning the patients and their relatives to request data not found in the medical records.

The primary objective of this study was disease-free survival rate of neoadjuvant CRT compared with adjuvant CRT. And the second objective was overall survival rate of neoadjuvant CRT compared with adjuvant CRT. The staging estimation of patients was made by using both clinical staging and pathological staging. Pathological staging was used with the patient group receiving adjuvant CRT, and both clinical and pathological staging was used with the patient group receiving neoadjuvant CRT. It depended on which one has higher staging, and stage II and III patients were especially considered to be included in this study.

The data was analyzed and calculated by using the statistical standards program. This was made by calculating mean, log-rank and hazard ratio analysis, Kaplan-Meier disease-free survival and overall survival curves by fixing P-value at lower than 0.05 which was significantly different when comparing the difference between two sample groups. This study has been

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria

Rectal carcinoma patients having adenocarcinoma type of tissue were stage II and III patients according to AJCC cancer staging 2002.

Exclusion criteria

Patients had other types of cancer, such as synchronous colonic cancer.

Patients had been treated by chemotherapy for other types of cancer which occurred before having rectal carcinoma.

Patients had congenital disease which caused severe difficulties in daily living (ASA status>III).

Patients who had clinical history of receiving radiotherapy for treating cancer previously occurred in other areas.

Patients who had received biopsy, and positive margin was found.

Table 2 Characteristics of patients

	Neoadjuvant CRT (n = 54)	Adjuvant CR (n = 71)	Student t-test and chi square
Mean age	54.7	57.3	0.214(T)
Tumor stage II	70.4 %	43.7 %	
Tumor stage III	29.6 %	56.3 %	0.003
Well-diff cancer	55 %	45 %	
Moderate-diff	40 %	48 %	
Poor-diff cancer	5 %	6 %	0.712
Chemotherapy: formula LV + 5-FU	74.1 %	88.7 %	
Chemotherapy: other formulae	25.9 %	11.3 %	0.034

research-ethically certified by the committee on ethical research of the National Cancer Institution.

Results

The patient number needed in statistical calculation to find out that disease-free survival rate of neoadjuvant CRT took longer time than adjuvant CRT with credibility power at 85%. When 5% loss follow up was permitted, the number of each sample group was equal to 290 patients.

During 1990-2009 there were 355 patients of rectal carcinoma who had been treated with radiotherapy at the National Cancer Institution. There were only 125 patients who had been selected for this study. Of these patients, the sample group 1 receiving neoadjuvant CRT consisted of 51 patients, and the sample group 2 receiving adjuvant CRT consisted of 74 patients.

The patients in neoadjuvant CRT group aged between 26-78 years with mean age at 54.7 years when compared with adjuvant CRT group aged between 33-83 years with mean age at 57.3 years, and there was no significant difference. The sample group 1 had more stage II cancer rate than the group 2, which was 70.4% to 43.7% with statistically significant difference. Both groups had equal tumor grading rate.

All patients in neoadjuvant CRT group had received chemotherapy together with radiotherapy before operation and had also received chemotherapy after the operation. Both patient groups had received full term radiotherapy. All patients had received high dose (4500-5000cGY) type of radiotherapy.

Most patients received 5-fluorouracil together with leucoverin: formula mayo or de Gramont (74.1% and 88.7% in group 1 and 2 respectively). Other formulae of chemotherapy for treating the patients were xeloda, FOLFOX, UFUR+leucoverin, etc. Chemotherapy formula (such as FOLFOX4) had been changed in some patients after cancer recurrence or spread to other organs was found.

Neoadjuvant CRT had statistically significant (95% confident interval, P=0.034) better disease-free survival rate than adjuvant chemoradiation treatment. The neoadjuvant CRT group had overall disease-free survival rate: 1 year at 94.2%; 2 years at 81.8%; 3 years at 70.4%; and 5 years at 70.4% compared with the adjuvant CRT group which had overall disease-free survival rate: 1 year at 82.4%; 2 years at 73.5%; 3 years at 57.1%; and 5 years at 46.1%, as shown in Table 3.

Table 3 Disease-free and overall survival

	NeoadjuvantCRT (%)	Adjuvant CRT (%)	p
Disease free survival			
1 year	94.2	82.4	
2 years	81.8	73.5	
3 years	70.4	57.1	
5 years	70.4	46.1	0.034
Overall survival			
1 year	96.2	89.7	
2 years	90.1	85.3	
3 years	82.1	69.9	
5 years	64.5	55.4	0.147

OS at 5 years of Group 1 was derived from value arising by comparing the rule of three.

Neoadjuvant CRT group tended to have non-statistically significant (95% confident interval, P=0.147) better survival rate than adjuvant CRT group. The neoadjuvant CRT group had overall survival rate: 1 year at 96.2%; 2 years at 90.2%; 3 years at 82.1%; and 5 years at 64.5% compared with the adjuvant CRT which had overall survival rate: 1 year at 89.7%; 2 years at 85.3%; 3 years at 69.9%; and 5 years at 55.4%, as shown in Table 3. When analyzing a particular sub-group of patients with stage II, it was found that disease-free survival rate and overall survival rate of both groups were not significantly different, as shown in Table 4.

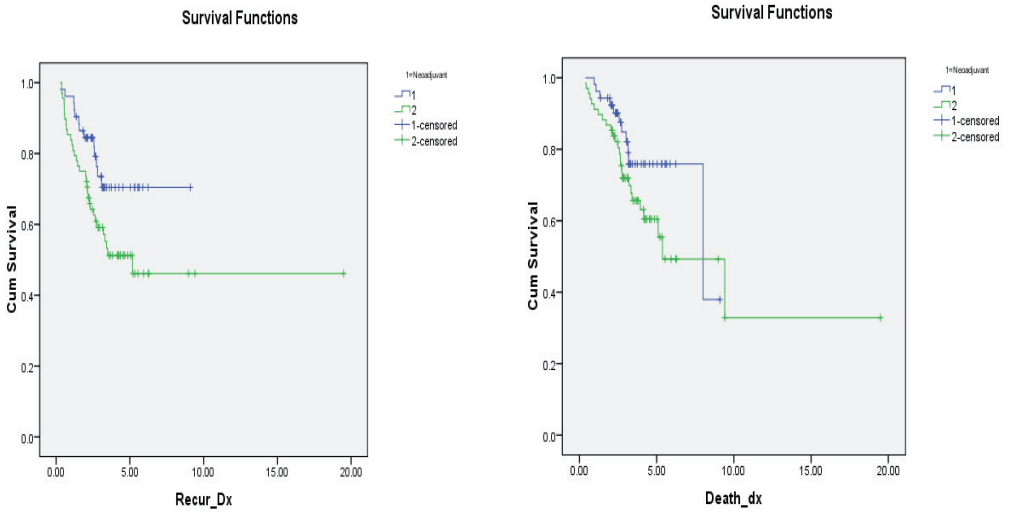
It was found in only stage III patients that the number of sample group was not enough to calculate the difference. However, the neoadjuvant CRT group

Table 4 Disease-free and overall survival of stage II patients

	NeoadjuvantCRT (%)	Adjuvant CRT (%)	p
Disease free survival			
1 year	91.9	91.5	
2 years	80.2	83.3	
3 years	64.7	67.4	0.527
Overall survival			
1 year	94.6	82.5	
2 years	91.1	78.0	
3 years	83.5	57.2	0.269

Table 5 Disease-free and overall survival of stage III patients only

	NeoadjuvantCRT (%)	Adjuvant CRT (%)	p
Disease free survival			
1 year	87.5	78.9	
2 years	80.8	63.2	
3 years	-	45.9	Not shown
Overall survival			
1 year	3.8	92.1	
2 years	79.1	84.2	
3 years	-	s60.4	0.269



Recurrence Death

Figure 1 Keplan-Meier curves of disease-free and overall survival in all patients without stage division (blue line = neoadjuvant group, green line = adjuvant group)

has better disease-free survival rate and overall survival rate when 1 year follow-up had been made (87.5 vs 78.9) and (93.8 vs 92.1) respectively, as shown in Table 5.

Discussions

This study provides the results comparable to studies by Stryker[1] and Sebag-Montefiore D[2]. The group with neoadjuvant CRT had better disease-free survival rate than the group with adjuvant CRT when 5-year follow-up had been made. The group with neoadjuvant CRT had no statistically significant better overall survival rate than the group with adjuvant CRT when 5-year follow-up had been made. Chemotherapy formula had been changed (mostly FOLFOX4) for both groups of patients whom cancer recurrence or distant metastasis was found. This might cause longer period of survival to the patients and be factors affecting the results of this study.

From the analysis on sub-group of rectal carcinoma patients stage III only, it was found that neoadjuvant CRT group had better disease-free survival rate than adjuvant CRT group at 1 year and 2 years. It was also found that after 2-year follow-up had been made, there were no patients in this group having recurrence or died. However, since the number of patients in this sub-group was smaller (16 patients in group 1 and 38

patients in group 2), the data thus were not sufficient to draw a conclusion to whether giving neoadjuvant CRT to stage II rectal carcinoma patients is better than giving adjuvant CRT to them.

The numbers of patients in neoadjuvant CRT group were 51 whereas adjuvant CRT group were 74. However, this study was designed that each group had equal number of 290 patients. The reason the patient's targeted number could not be achieved was that this study was conducted in a single center (the National Cancer Institution) causing less credibility to this study. The staging of neoadjuvant CRT patients had been estimated in two methods: before operation, they had been estimated by clinical finding and CT finding; and after operation, they had been estimated by operative finding and pathological finding. As a result, there might be some stage III patients having been estimated to be in stage II since lymph node metastasis had not been found during CT (before operation) and lymph node metastasis had not been found during pathological finding either (because of the CRT results).

Another limitation of this study was due to a retrospective manner with several uncontrollable factors occurred. For example, the patients had different chemotherapy regimens or different operative procedures. However, chemotherapy formulas given were the standard regimens and surgeons made standard operations (TME had also been made to all operations and the biopsy results showed free margin).

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