RESEARCH ARTICLE

Outcomes of Preoperative Chemoradiotherapy and Combined Chemotherapy with Radiotherapy Without Surgery for Locally Advanced Rectal Cancer

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Abstract

Purpose: To evaluate the treatment outcomes of patients with locally advanced rectal cancer treated with preoperative concurrent chemoradiotherapy (CCRT) or combined chemotherapy together with radiotherapy (CMT-RT) without surgery. Materials and Methods: A total of 84 patients with locally advanced rectal adenocarcinoma (stage II or III) between January 1st, 2003 and December 31st, 2013 were enrolled, 48 treated with preoperative CCRT (Gr.I) and 36 with combined chemotherapy and radiotherapy (CMT-RT) without surgery (Gr.II). The chemotherapeutic agents used concurrent with radiotherapy were either 5-fluorouracil short infusion plus leucovorin and/or capecitabine or 5-fluorouracil infusion alone. All patients received pelvic irradiation. Results: There were 5 patients (10.4%) with a complete pathological response. The 3 year-overall survival rates were 83.2% in Gr.I and 24.8 % in Gr.II (p<0.01). The respective 5 year-overall survival rates were 70.3% and 0% (p<0.01). The 5 year-overall survival rates in Gr.I for patients who received surgery within 56 days after complete CCRT as compared to more than 56 days were 69.5% and 65.1% (p=0.91). Preoperative CCRT used for 12 of 30 patients in Gr.I (40%) with lower rectal cancer demonstrated that in preoperative CCRT a sphincter sparing procedure can be performed. Conclusions: The results of treatment with preoperative CCRT for locally advanced rectal cancer showed comparable rates of overall survival and sphincter sparing procedures as compared to previous studies.

Keywords: Concurrent chemoradiotherapy - rectal cancer - outcome - Thailand

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Introduction

Colorectal cancer is a common malignancy in the USA, Europe and Asian countries, which may be correlated with westernized lifestyle. (Safaee et al., 2008; Mostafa et al., 2011; Afzaninawati et al., 2012; Terek et al., 2012). In the past decades, colorectal cancer was not common in Thailand, but in recent years, the incidence of rectal cancer has been increasing in both males and females.(Sriplung et al., 2006; Suwanrungruang et al., 2006; Khuhaprema and Srivatanakul, 2008). The age-standardized incidence rates (ASR) of colorectal cancer in Thailand between years 2007-2009 was 14.7:100,000 in males and 11.0 :100,000 in females. (Khuhaprema et al., 2013). The gold standard treatment for locally advanced rectal cancer is a combination of surgery, chemotherapy and radiation therapy.

Some of the reports showed the advantages of preoperative CCRT over postoperative CCRT in terms of an increased rate of complete pathological response and local control (Bosset et al., 2006; Bujko et al., 2006; Gerard et al., 2006). This present study was designed to evaluate the outcomes of preoperative CCRT and combined CMT-RT without surgery for locally advanced rectal cancer.

Materials and Methods

The 84 patients with locally advanced rectal cancer (stage II, III) who were treated by preoperative concurrent chemoradiotherapy (CCRT) or CMT-RT without surgery between January 1st, 2003 and December 31st, 2013 were retrospectively reviewed. The study was approved by the Ethics Committee for Human Research of Khon Kaen University, HE 571382. The patient data were collected from medical records of radiotherapy unit, outpatient department cards, the cancer unit of Srinagarind hospital, Faculty of Medicine , KKU, Thailand, patient data records from Praxtical program and patient registrations from public official records. Inclusion criteria: 1. Locally advanced rectal cancer (stage II-III, T3-4 or regional node positive and no distant metastasis (M0)) confirmed

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by CT/MRI imaging. 2. Histologically confirmed adenocarcinoma of the rectum. 3. Received preoperative CCRT followed by surgery (low anterior resection (LAR) or abdominoperineal resection (APR) or CMT-RT without surgery. Exclusion criteria;1. Incomplete data to analysis such as no previous biopsy to confirm histopathological diagnosis before treatment, loss of medical records, no previous CT/MRI imaging to confirm staging of cancer before treatment. 2. Multiple primary cancers developed during treatment. 3. Developed distant metastasis during treatment. 4. Previous radiotherapy in the pelvic area.

The total of 114 patients with locally advanced rectal cancer were treated by CCRT or CMT-RT. Of the 30 patients who were excluded, 20 patients had incomplete data, 9 patients developed distant metastasis during treatment and one had double primary cancers. 84 patients, then, were eligible and enrolled in this study and were entered into two groups: 48 patients in group I (Gr.I) who received preoperative CCRT followed by surgery and 36 patients into group II (Gr.II) who only received CMT-RT and without surgery.

The radiotherapy techniques used in this study were conventional radiotherapy. All patients received daily radiotherapy 1.8-2 Gy/fraction to a total dose of 40-50.4 Gy with or without a coned boost to primary tumors. Chemotherapy was given as bolus 5-Fluorouracil (5FU) 400 mg/m^2/day plus leucovorin (LV) 20 mg/m^2/day, 4 days/cycle concurrent with radiotherapy in the 1st week and the 5th week or capecitabine 825 mg/m^2 twice daily concurrent with radiotherapy 5 days /week. The other chemotherapy regimens were continuous infusions 5FU or a short infusion of 5FU alone.

Statistical analysis

Overall survivals (OS) were calculated from the date of the end of CCRT to the date of death or last follow-up and plotted as Kaplan-Meier curves. A p value of <0.05 was considered to be statistically significant.

Results

Patients and treatment characteristics

From the enrolled 84 patients, 48 patients (57.1%) in Gr.I received preoperative CCRT followed by surgery and 36 patients (42.9%) in Gr.II received combined CMT-RT without surgery. The median follow-up times were 3.7 years (range 3.1 months - 10.9 years) in Gr.I and 9.3 months (range 8 days to 4.5 years) in Gr.II. Patient and treatment characteristics are shown in Table 1.

Outcomes

1. Pathological response rate: In preoperative CCRT (Gr.I), the pathological response was defined by comparing the staging diagnosis from CT / MRI imaging before treatment and the pathological findings of the specimens obtained from surgery. There were 5 patients (10.4%) who were found to have complete pathological responses.

2. Radiological response rates: In order to evaluate the radiological response rate according to RECIST criteria. (Eisenhauer et al., 2009) There were 58.3% (28/48 cases) in Gr.I and 47.2% (17/36 cases) in Gr.II. who had the CT/MRI imaging within 4-6 weeks after complete CCRT

Table 1. Patients and Treatment Characteristics

Patients and treatment characteristics	Treatment	
	Gr.I : Cases (%)	Gr.II : Cases (%)
Total number	48 (57.1)	36 (42.9)
Gender		
Male	26 (54.2)	23 (63.8)
Female	22 (45.8)	13 (26.2)
Age (yrs) : Median (range)	56 (20-80)	59.5 (29-84)
< 20	1 (2.1)	0
21-40	8 (16.6)	4 (11.1)
41-60	25 (52.1)	15 (41.7)
>60	14 (29.2)	17 (47.2)
KPS (%) : Median	90	80
100	10 (20.8)	2 (5.6)
90	24 (50.0)	8 (22.2)
80	13 (27.1)	17 (47.2)
< 70	1 (2.1)	9 (25.0)
Underlying disease		
No	39 (81.3)	22 (61.2)
Yes	9 (18.7)	14 (38.9)
Sites of tumors		
Upper	10 (20.8)	7 (19.4)
Middle	8 (16.7)	7 (19.4)
Lower	30 (62.5)	19 (52.8)
Whole rectum	0	3 (8.3)
TNM staging		
IIA	10 (20.8)	2 (5.5)
IIB	0	0
IIC	2 (4.2)	0
IIIA	1 (2.1)	0
IIIB	20 (41.7)	20 (55.6)
IIIC	15 (31.2)	14 (38.9)
Chemotherapy regimens		
5FU +LV	20 (41.7)	21 (58.3)
Capecitabine	27 (56.1)	15 (41.7)
Other	1 (2.1)	0
Radiation dose (Gy)		
45 - <50	18 (37.5)	1 (2.8)
50 - 50.4	26 (54.2)	35 (97.2)
> 50.4	4 (8.3)	0
TNM downstaging after CCRT (evidenced by imaging)	28	
Yes	21 (75)	
No	7 (25)	
TNM downstaging after combined CMT-RT (evidenced by imaging)		17
Yes		7 (41.2)
No		10 (58.8)
Time interval between CCRT and surgery (days)		
< 56 (Median 43 , range 31-56)	22 (45.8)	
> 56 (Median 77, range 61-108)	26 (54.2)	
Types of surgery		
LAR	30 (62.5)	
APR	18 (37.5)	
Follow up times, mean	3.7 yrs.	9.3 mo.
Range	(3.1 mo. - 10.9yrs.)	(8 d – 4.5 yrs.)

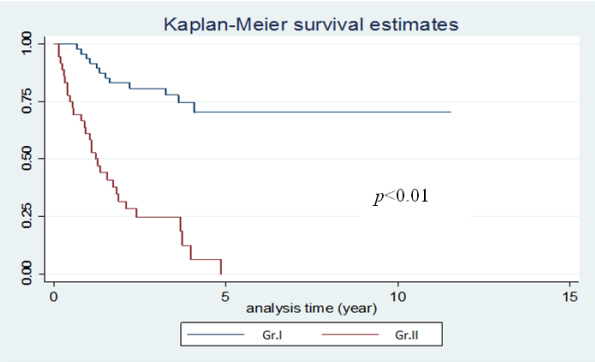

Figure 1. Overall Survival Curves between Preoperative CCRT plus Surgery(Gr.I) and CMT-RT without Surgery (Gr.II)

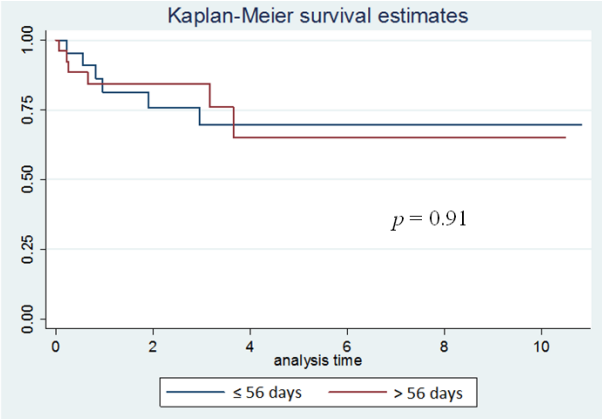

Figure 2. Overall Survival Curves in Gr.I According to Time Intervals from Preoperative CCRT to Surgery ≤56 Days and > 56 Days

treatment. The results revealed a complete radiological response rate was 7.2 % (2 cases) in Gr.I and 5.8% (1 case) in Gr.II. The non-complete radiological response rate 92.8% (26 cases) in Gr.I and 94.2% (16 cases) in Gr.II.

3. Sphincter sparing procedure rate: From the 30 patients in Gr.I with lower rectal cancer, 12 patients (40%) had a preserved sphincter by using the low anterior resection technique.

Overall survival rates

The 3 year overall survival rates between Gr.I and Gr.II were 80.7% and 24.8 % (p<0.01) and 5 year-overall survival rates in Gr.I and Gr.II were 70.3% and 0 % (p<0.01) as shown in Figure 1.

In the Gr.I, group, the 5 years overall survival rate between the patients who received surgery within 56 days after complete preoperative CCRT and more than 56 days were 69.5% and 65.1% (p=0.91) as shown in Figure 2.

Discussion

Preoperative CCRT is the standard of care in locally advanced rectal cancer. The results from randomized studies of preoperative versus postoperative CCRT support the preoperative treatment approach (Sauer et al., 2004; Roh et al., 2009; Park et al., 2011). The advantages of preoperative CCRT over postoperative CCRT were improved tumor down staging, improved local control, increased rate of sphincter sparing surgery and fewer acute and late toxicities than were previously reported (Sauer et al., 2004; Bosset et al., 2006; Bujko et al., 2006; Gerard et al., 2006). The results of this present study demonstrated the complete pathological response rate of 10.4% (5 cases) in preoperative CCRT (Gr.I). The preoperative CCRT arm of many trials showed the complete pathological response rate of 8-14% (Sauer et al., 2004; Bosset et al., 2006; Bujko et al., 2006; Gerard et al., 2006). The successful sphincter sparing procedure rate in Gr.I of this study was 40% which was similar to a previous study (Sauer et al., 2004).

The 5 year overall survival rate in Gr.I in this study was 70.3% which was comparable to a previous study (Gerard et al., 2006). In subgroup analysis of Gr.I, the 5 year overall survival rates of the patients who received surgery after complete CCRT within 56 days versus more than 56 days were 69.5% and 65.1% and were not statistically significant. (p=0.91). The 3 year overall survival rates of 90.2% in patients who underwent surgical resection less than 8 weeks and 87.2% in greater than 8 weeks were similarly previously reported (Jeong et al., 2013).

One report showed the 5 year overall survival rates of 81.7% in preoperative CCRT and 89.2% in postoperative CCRT (Pichayada et al., 2015). In contrast, the 5 year overall survival rates of colorectal cancer in Asian countries were about 60% (Park et al., 1999; Shiono et al., 2005; Moghimi et al., 2008). This study demonstrated the 3 year overall survival rates of 80.7% in Gr.I and 24.8 % in Gr.II. (p<0.01). The 5 year overall survival rates of 70.3% in Gr.I and 0 % Gr.II (p<0.01) were significantly different. These findings indicated that combined CMT-RT without surgery by radiation doses of 45-50.4 Gy may be not adequate and resulted in significant inferior survival rates as compared with preoperative CCRT followed by surgery. The patients in Gr.II had many unfavorable factors, some of which, precluded them from surgical treatment.

There were 2/28 patients (7.2%) in Gr.I who demonstrated complete radiological responses. The first patient was classified as T4bN1M0 (stage IIIC) by preoperative CT scan while the pathological staging was classified as T2N0M0 (stage I) and the time interval between complete CCRT to surgery was 43 days. The second patient was classified as T3N1M0 (stage IIIB) by preoperative CT scan while the pathological staging was classified as T2N0M0 (stage I) and the time interval between complete CCRT to surgery was 42 days. Nevertheless, the accuracy of CT/MRI imaging for tumor staging has been shown to be approximately 50-70% and nodal staging approximately 50-75% (Bruce D. Minsky et al., 2012). There may be some variations of image interpretation between machines, techniques, timing and radiologists. (Yang et al., 2005; Lee et al., 2013). Even so, in the patients with complete radiological response, surgery should not be omitted because some residual tumor may not be visualized on CT/MRI imaging.

In conclusion, the results of treatment with preoperative CCRT for locally advanced rectal cancer showed comparable rates of overall survival and sphincter sparing procedure as compared to previous studies.

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