Original Article

Outcomes of Neoadjuvant Chemoradiation Therapy for Locally Advanced Rectal Cancer: The Effect of Preoperative Chemoradiotherapy Followed by Additional Chemotherapy on Advanced Rectal Cancer

Pi-Kai Chang
Shu-Wen Jao
Chang-Chieh Wu
Chia-Cheng Lee
Tsai-Yu Lee
Cheng-Wen Hsiao
Division of Colon and Rectal Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Key Words
Advanced rectal cancer;
Neoadjuvant concurrent chemoradiotherapy;
Tumor downstaging;
Local recurrence

Background. In most cases of locally advanced rectal cancer, neoadjuvant chemoradiation therapy (CCRT) reduces tumor size and results in histopathologic downstaging. This results in improved long-term oncologic outcomes. Pathologic complete remission ranges from 8% to 19%, depending on the regimen and dose of chemotherapy and/or radiotherapy.
Patients and Methods. We retrospectively reviewed the medical records of patients diagnosed with rectal adenocarcinoma who were receiving neoadjuvant CCRT and curative surgery in our hospital from January 2005 to December 2008. The regimen of neoadjuvant CCRT included a high weekly dose of 5-fluorouracil (5-FU) (2000 mg/m^2 5-FU for 24 hours plus 500 mg/m^2 leucovorin intravenously for 2 hours), concurrent with radiotherapy at a total dose of 4500 cGy. Chemotherapy was continued until 2 weeks before surgery, and patient underwent surgery within 6 to 8 weeks of completing CCRT.
Result. In total, 61 patients, including 31 males and 30 females with an average age of 67.6 years were examined. Most patients had a good response to neoadjuvant CCRT and experienced tumor downstaging. Only 15 patients did not experience a change in disease stage after neoadjuvant CCRT. The non-responding group had a significantly lower curative resection rate (R0 resection rate) ($p = 0.04$) and higher local recurrence rate ($p = 0.03$) than the responding group.
Conclusion. Neoadjuvant CCRT for locally advanced rectal cancer can result in tumor downstaging and shrinkage. The regimen, dosage, and duration of chemotherapy were variable. Our results demonstrate that the administration of chemotherapy until 2 weeks before curative surgery was safe, however, the effect on the pathological complete response rate requires additional study.
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Correspondence to: Dr. Tsai-Yu Lee, Division of Colon and Rectal Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Cheng-Kung Road, Section 2, Taipei 114, Taiwan. Tel: 886-2-8792-3311; Fax: 886-2-8792-7411; E-mail: lee-tsai-yu@yahoo.com.tw

Total mesorectal excision is a major treatment strategy for rectal cancer. Total mesorectal excision involves a sharp dissection of the rectosacral fascia, and excision of the rectum and mesorectum at the level of the levators. Total mesorectal excision of resectable rectal cancekr reduces the local recurrence rate to 5% to 10%.[1,2] However, local recurrence remains a concern in the treatment of locally advanced, fixed rectal cancers. Consequently, preoperative concurrent chemoradiotherapy (CCRT) was added to the treatment regimen for locally advanced rectal cancer. Preoperative CCRT decreases local recurrent rates and reduces general toxicities.[3-5] In most cases, neoadjuvant chemoradiation therapy results in a reduction in tumor size, increased tumor mobility, and histopathologic downstaging, which improves long-term oncologic outcomes. However, tumor response to CCRT is variable. Pathologic complete remission can range from 8% to 19%, depending on the regimen and dose of chemotherapy and/or radiotherapy.[6-9] In general, locally advanced rectal cancer is first treated with neoadjuvant CCRT, which is followed by surgery that is performed approximately 6 to 8 weeks later. In our hospital, we routinely prescribe additional cycles of chemotherapy after CCRT during the interval between complete CCRT and surgery. In the present study, we report the clinical outcome, pathological staging, and experiences with our CCRT regimen in patients who underwent neoadjuvant chemoradiotherapy followed by curative resection for locally advanced rectal cancer.

Patients and Methods

We retrospectively reviewed the medical records of patients diagnosed with rectal adenocarcinoma, who were receiving neoadjuvant CCRT and surgery at our hospital from January 2005 to December 2008. Cases with tumor obstruction and metastasis were excluded. Patients who only underwent local excision were also excluded. The diagnosis of rectal adenocarcinoma was confirmed by sigmoidoscopic biopsy. T staging was performed by transrectal ultrasonography and N staging was performed by pelvic computed tomography (CT). Patients with lesions of stage T3 or greater were defined as locally advanced rectal cancers. In all patients, CT was used to evaluate the occurrence of distant metastasis. Clinical data including age, local recurrence, curative resection (R0 resection), postoperative complications, gender, preoperative clinical stage, postoperative pathological stage, and oncological outcome were analyzed.

Neoadjuvant CCRT for rectal cancer in our hospital consisted of a high weekly dose of 5-fluorouracil (5-FU) (2000 mg/m^2 5-FU for 24 hours plus 500 mg/m^2 leucovorin intravenously for 2 hours), concurrent with radiotherapy, at a total dose of 4500 cGy (180 cGy/day, 5 days per week, for 5 weeks). Chemotherapy was continued until 2 weeks before surgery, and patients underwent surgery within 6 to 8 weeks of completing CCRT. Clinical response was evaluated post-CCRT by CT, sigmoidoscopy, and digital rectal examination. The overall response rate was 75%; 11 (18%) of patients experienced a complete response and 35 (57%) patients experienced a partial response.

All statistical analyses were performed using the SPSS version 17.0 software for Windows (IBM, New York, USA). The significance level of 5% was used for all analyses. We analyzed the differences in the factors that may predict complete, partial, or non-response by using ANOVA test, Person's Chi-Square test, and Fisher's exact test. In our analyses of disease-free survival, curative surgery, and recurrence, the complete response group was combined with the partial response group.

Results

The characteristics of all patients are shown in Table 1. All patients underwent exploratory laparotomy with total mesorectal excision (TME), whereas only some patients underwent protective ileostomy. In total, we analyzed 61 patients, including 31 males and 30 females, with an average age of 67.6 years (range, 33-100 years). The preoperative clinical staging of the patients indicated stage II in 18 and stage III in 43 patients. After neoadjuvant CCRT, all the included patients underwent surgery. The final pathological staging indicated complete remission (n = 11, 18%), stage

Table 1. Patient characteristics

Patient characteristics	
Age (years)	67.6
Sex	
Male	31
Female	30
Performance status	
0	42
1	14
2	05
Tumor location	
U[1]	11
M[2]	17
L[3]	33
Pre op Clinical stage	
II	18
III	43
ASA[4] score	
1	33
2	18
3	10

1. U: upper; 2. M: middle; 3. L: lower; 4. ASA: The American Society of Anesthesiologists.

0 (n = 2, 3.2%), stage I (n = 16, 26.2%), stage II (n = 21, 34.4%), and stage III (n = 11, 18%). Most of the patients had a good response to neoadjuvant CCRT and experienced tumor downstaging. Only 15 patients exhibited no change in disease stage after neoadjuvant CCRT. The overall anastomotic leakage rate was 3.2%.

As shown in Table 2, age (p = 0.15), sex (p = 0.94), leakage (p = 0.43), surgical complications (p = 0.91), tumor level (p = 0.15), 3-year disease-free survival (p = 0.09), pre-CCRT clinical staging (p = 0.43), and histologic type (p = 0.76) were not statistically different within each group. The non-responding group (80%) had a lower curative resection rate (R0 resection rate) as compared to the responding group (97.8%), and this difference was statistically significant (p = 0.04). The local recurrence rate was significantly higher (p = 0.03) in the non-responding group (26.7%) than in the responding group (4.3%). In addition, the overall recurrence rate was significantly higher (p = 0.03) in the responding group (8.7%) than in the non-responding group (33%). Fig. 1 shows the cumulative disease-free survival rate and Fig. 2 shows the cumulative local recurrence rate.

Discussion

Miles[10] first developed abdominoperineal resection in the early 1900s for complete resection of rectal cancer. With the technological development in surgical devices, Heald et al.[11] introduced TME in 1982, which allowed for sphincter preservation and a decrease in rectal cancer local recurrence rates. However, patients with advanced rectal cancer have a higher incidence of local recurrence after surgery. One study,[12] which analyzed 14 randomized and controlled trials, found that short course preoperative radiotherapy followed by total mesorectal excision for resectable rectal cancer improved local recurrence rates compared to surgery alone. However, this treatment course did not improve the survival rate.[13] At present, neoadjuvant chemoradiotherapy is widely used for advanced rectal adenocarcinoma to facilitate anal sphincter preservation and decrease the rate of local recurrence. The aim of this treatment is to achieve tumor downstaging and shrinking, thereby improving curative surgical resection and long-term oncologic outcome.

In the present study, 61 patients received neoadjuvant CCRT and were followed-up for at least 3 years. The overall recurrence rate was 13.1%, including 0% in the complete response group, 8.6% in the partial response group, and 45.4% in the non-response group. The overall curative resection rate was 93.4%, including 100% in the complete response group, 97.1% in the partial response group, and 80% in the non-response group (p = 0.04).

For neoadjuvant CCRT, we used the widely accepted chemotherapy regimen of 5-FU plus leucovorin by continuous infusion,[14-17] and the toxicity was tolerable. In addition, benefits of using oxaliplatin or irinotecan for neoadjuvant CCRT has also been reported[18-21] with a pathological complete response (pCR) rate of 14-28%. However, the long- term outcomes with this therapy were unremarkable. Major toxicities due to chemotherapy included grade 3 nausea and vomiting (12%), grade 2 mucositis (7%), and grade 3 diarrhea (18%). In most previous studies, a resting period was maintained after the patients completed CCRT; however, in the present study, we

Table 2. CCRT Response comparison

	Complete response	Partial response	Non response	*p*-value
Age	70.3 ± 16.6	69.9 ± 14.4	60.3 ± 20.1	0.15
Sex				0.94
Male	7 (60%)	15 (57%)	9 (64%)	
Female	4 (40%)	20 (43%)	6 (36%)	
Surgical complication	1 (9%)	5 (14%)	2 (13%)	0.91
Surgical site infection	1	3	1	
Intestinal obstruction	0	1	0	
Pneumonia	0	0	1	
Urinary tract infection	0	1	0	
Leakage	0	1 (3%)	1 (7%)	0.43
DFS (3 years)[1]	11 (100%)	31 (89%)	11 (73%)	0.09
Tumor level				0.15
Low	5 (46%)	23 (66%)	5 (33%)	
Middle	5 (46%)	6 (17%)	6 (40%)	
upper	1 (8%)	6 (17%)	4 (27%)	
Pre CCRT Clinical stage				0.43
Stage II	4 (36%)	8 (23%)	6 (40%)	
Stage III	7 (64%)	27 (77%)	9 (60%)	
Histologic type				0.76
Well	3 (27%)	5 (14%)	1 (7%)	
Moderately	7 (64%)	26 (74%)	12 (80%)	
Severe	1 (9%)	4 (12%)	2 (13%)	
Curative surgery (R0 resection)	11 (100%)	34 (97%)	12 (80%)	0.04
Operative method				0.59
LAR[2]	10 (91%)	31 (89%)	12 (80%)	
APR[3]	1 (9%)	4 (11%)	3 (20%)	
Local recurrence	0	2 (6%)	4 (27%)	0.03
Distant metastasis	0	2 (6%)	3 (20%)	0.09
Overall recurrence	0	4 (11%)	5 (33%)	0.03

1. DFS (3 years): disease free survival for more than 3 years.
2. LAR: low anterior resection.
3. APR: abdominioperineal resection.

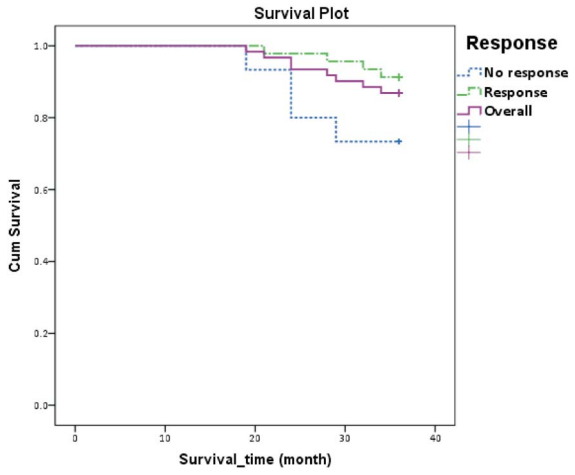

Fig. 1. Cumulative disease free survival rate in groups of overall, no response to CCRT, response to CCRT.

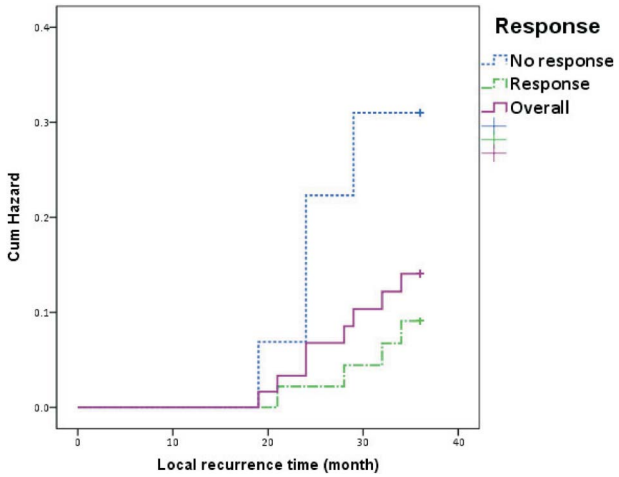

Fig. 2. Cumulative local recurrence rate in groups of overall, no response to CCRT, response to CCRT.

continued administering chemotherapy until 2 weeks before surgery. We believe that the chemotherapy regimen used in the present study had a favorable outcome and tolerable toxicity despite the absence of a resting period. The oncological benefit of the additional chemotherapy was not well described in this study because of the lack of a control group. A recent study[22] reported that additional chemotherapy after CCRT was well tolerated and may increase the pCR rate without increasing the surgical complication rates. Moreover, due to lack of a control group in our study, we cannot properly explain whether there is benefit with additional chemotherapy after CCRT.

The dose and duration of radiation varies across different studies. Urso et al.[23] reported that a dose of 50.4 Gy in preoperative radiotherapy may increase the rate of late major complications. Mohiuddin et al.[24] reported that the pCR rate was associated with the dosage of preoperative radiotherapy. In the present study, most patients tolerated the total 4500 cGy radiation dose well, and experienced an acceptable oncological outcome.

Conclusion

Neoadjuvant CCRT for locally advanced rectal cancer can result in tumor downstaging and shrinkage. The regimen, dosage, and duration of chemotherapy were variable. Our results demonstrate that the administration of chemotherapy until 2 weeks before curative surgery was safe; however, the effect on the pCR rate requires additional study. Patients with a tumor response after CCRT experienced better local recurrence rates and curative resection rates than patients who did not respond to CCRT.

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原　著

局部侵犯性直腸癌的術前輔助電化療的預後報告：術前輔助電化療結束後，額外追加化療之治療成效

張筆凱　饒樹文　吳昌杰　李家政　李才宇　蕭正文

國防醫學院　三軍總醫院　外科部　大腸直腸外科

背景　局部侵犯性直腸癌患者經術前輔助電化療後，大部分患者可達到腫瘤縮小及降低腫瘤分期等效果。對其腫瘤之局部復發率也有明顯之降低的效果。病理上的病理完全反應率大約是百分之八到十九，根據其使用之化療藥物及放療劑量不同而有差異。

方法　回溯性病例回顧於 2005 年一月至 2008 年十二月，經診斷為直腸癌且接受術前輔助電化療及腫瘤根治性手術的患者。術前輔助電化療的處方為高劑量 5FU (每體表面積 2000 毫克) 靜脈滴注 24 小時加上 leucovorin (每體表面積 500 毫克) 靜脈滴注兩小時，及總計量 4500cGy 的放射治療。病人術前輔助電化療結束後 6-8 週接受手術，但化療持續至手術前兩週。

結果　61 位患者中有 31 個男性，30 女性。平均年齡為 67.6 歲。大部分的患者對於術前輔助電化療的反應良好，有降低腫瘤分期。只有 15 位患者腫瘤對術前輔助電化療沒有反應。對於術前輔助電化療後沒有反應的患者，與術前輔助電化療後腫瘤期別下降的患者相較之下，有較低的根治性切除比例與較高的局部復發率，並達到統計學上意義。

結論　術前輔助電化療對於局部侵犯的直腸癌患者，可提供腫瘤期別下降及腫瘤縮小之效果。術前的化療的藥物，劑量及持續期間並無定論，根據我們的經驗，持續化療至術前兩週是安全無虞的，而其對於病理上腫瘤完全緩解機率的影響則需更多的研究證實。

關鍵詞　局部侵犯性直腸癌、術前輔助電化療、降低腫瘤分期、局部復發率。