Original Article

Oxaliplatin-based Neo-adjuvant Concurrent Chemo-radiotherapy in Treating Locally Advanced Lower Rectal Cancer

Yen-Hao Chen[1]
Hwei-Ming Wang[1]
Joe-Bin Chen[1]
Da-Shin Chou[1]
Hsiu-Feng Mar[1]
Chou-Chen Chen[1]
Fang-Fan Chiang[1]
Chia-Ming Twu[2]

[1]*Department of Surgery, Colorectal section, Taichung Veterans General Hospital, Taichung*

[2] *Department of Surgery, Chia-yi Veteran hospital, Chia-yi, Taiwan*

Key Words
Locally advanced rectal cancer;
Neo-adjuvant concurrent chemo-radiotherapy;
Pathologic response;
Circumferential margin

Purpose. Lower advanced rectal cancer, for surgeons, is problematic. Neo-adjuvant concurrent chemo-radiotherapy, described in last decade, leads local control at high percentage of R0 resection and pathologic response rate with compactable results in our published journal.[1] Addition of oxaliplatin to 5-FU/leucovorin has been proposed because of evidence of improved disease-free and overall survival in patients with stage III colon cancer.[2,3] We hypothesized whether by adding Oxaliplatin to CCRT regimen, better results could be achieved.

Methods. From January 2008 to November 2008, 22 patients with locally advanced lower rectal cancer receiving Oxaliplatin-based Neo-adjuvant CCRT were enrolled for study group. From January 2005 to June 2007, 43 patients with locally advanced rectal cancer receiving non-Oxaliplatin-based Neo-adjuvant CCRT were enrolled for control group. Factors including circumferential margin and pathologic response rate were evaluated.

Results. Three patients, not receiving post-CCRT curative resection were excluded. Pathologic response rate was 100%; complete response rate: 31.6% & partial response rate: 68.4% respectively. Oxaliplatin based group had a better pathologic response rate versus non-Oxaliplatin based group (100% vs. 79.1%, $p = 0.047$) and excellent results in complete pathologic response (31.6% vs. 11.6%, $p = 0.031$) and an improved circumferential margin rate (94.7% vs. 90.7%, $p = 1.00$). Oxaliplatin based group had shorter stays (9.00 ± 3.96 vs. 11.47 ± 4.75, $p = 0.003$) and less anastomosis leakage (5.3% vs. 27.8%, $p = 0.075$).

Conclusion. Oxaliplatin-based Neo-adjuvant CCRT gives locally advanced lower rectal cancer patients more favorable results without increasing complications.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2010;21:17-22*]

Colorectal cancer is the most-common cancer in Taiwan and is a major cause of morbidity and mortality all over the world. Lower advanced rectal cancer, a challenge for surgeons, is problematic. Surgical therapy for rectal cancer has evolved since Ernest Miles first described the abdominoperineal resection in 1908.[4] By the 1920s, he had reduced the recurrence rate from almost 100% to approximately 30%,[5] thus ensuring this technique was the gold standard at that time while advocating extensive aggressive can-

Received: May 21, 2009. Accepted: September 10, 2009.

Correspondence to: Dr. Hwei-Ming Wang, Section of Colorectal surgery. Department of Surgery, Taichung Veterans General Hospital, No. 160, Sec. 3, Chung-Kang Rd, Taichung 407, Taiwan. Tel: +886-4-2359-2525 ext. 5160; Fax: +886-4-2350-0920; E-mail: WHM@vghtc.gov.tw

cer therapy. In retrospect, it is perplexing that such extreme surgery was standard, given its considerable local failure rate and its potential to result in urinary, sexual, and gastrointestinal dysfunction. Several modifications were proposed to promote loco-regional control and survival, with little success.[6,7] Improved suture material, including devices enabling low anastomosis, led to a shift toward sphincter-saving approaches with respect to cancer of the rectum. Anterior resection replaced abdomino-perineal resection as the mainstay of therapy, although adequate consideration of circumferential margins and lymph node harvests were often neglected by early reports in the 1950s. Not surprisingly, there was concern that sphincter-saving surgery might increase local recurrence. It was in this setting that total meso-rectal excision (TME) was first described in 1982 by Heald and colleagues,[8] which reduced recurrence rate to less then 10%.[9] Neo-adjuvant concurrent chemo-radiotherapy (CCRT), described in the last decade, leads local control for advanced rectal cancer at a higher percentage of R0 resection (margin clear under microscopic examination) and a lower recurrence rate.[10]

We had published a previous paper[1] that demonstrated Neo-adjuvant CCRT giving locally advanced lower rectal cancer patients more favorable results without increasing toxicity or complications. The addition of oxaliplatin to 5-FU/leucovorin adjuvant therapy has been proposed because of the evidence of improved disease-free survival and overall survival in patients with stage III colon cancer.[2,3] Moreover, some published papers[14-16] have provided the new idea of adding Oxaliplatin or Irontecan (Campto) into a pre-CCRT regimen might increase efficacy. Thus, in this study, we added Oxaliplatin to our previous CCRT regimen and sought further results than our previous study.

Methods

From January 2008 to November 2008, twenty-two patients with locally advanced (fixed tumor by digital rectal exam or T3-4 tumor by MRI/computer tomography) rectal cancer receiving preoperative CCRT were reviewed and enrolled for study group. From January 2005 to June 2007, forty-three patients with locally advanced (fixed tumor by digital rectal exam or T3-4 tumor by MRI/computer tomography) rectal cancer receiving non-Oxaliplatin-based preoperative CCRT were enrolled for control group.[1] The general parameters, such as age, sex, operative procedures etc., of both groups did not have significant difference, as shown in Table 1-1 and 1-2. The Oxaliplatin based Neo-adjuvant CCRT regimen for locally advanced lower rectal cancer in our hospital was 5-Fluorouracil 400 mg/M^2 plus leucovorin 20 mg/M^2, intravenously for one hour, on days 1-4 and 29-32, Oxaliplatin 85 mg/M^2, intravenously for two hours, on days 1-15-29, concurrent with radiotherapy (200cGy per day, Monday to Friday for five weeks).

Pathologic regression grading (PRG) was definite according to the grading system of tumor regression proposal (Dworak O. et al., 1997),[17] as follows: Grade 0: no regression; Grade 1: dominant tumor mass with obvious fibrosis and/or vasculopathy; Grade 2: dominantly fibrotic changes with few tumor cells or groups (easy to find); Grade 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; Grade 4: no tumor cells, only fibrotic mass (total regression or response). Tumor pathologic regression grade 1-3 means partial

Table 1-1. Oxaliplatin-based Neo-adjuvant CCRT patient characteristics

Age (y/o)	59.11 ± 11.04[a] 55.33 (26.41, 76.41)[b]	
	N	%
Sex		
Male	10	52.6
Female	9	47.4
DM		
+	4	21.1
-	15	78.9
Liver/Lung/Kidney		
+	1	5.3
-	18	94.7
Schedule		
APR	5	26.3
TME+1oop ileostomy	14	73.7
Lap/open		
Laparoscopy	16	84.2
Open	3	15.8

[a] Mean ± standard deviation.
[b] Median (range)

Table 1-2. Non-oxaliplatin-based Neo-adjuvant CCRT patient characteristics

Age (y/o)	55.57 ± 13.10[a] 41.28 ± 27.11[a]	
	N	%
Sex		
Male	22	51.2
Female	21	48.8
DM		
+	5	11.6
-	38	88.4
Liver/Lung/Kidney		
+	10	23.3
-	33	76.7
Cardiovascular		
+	10	23.3
-	33	76.7
Schedule		
APR	11	25.6
TME+1oop ileostomy	32	74.4
Lap/open		
Laparoscopy	25	58.1
Open	18	41.9

[a] Mean ± standard deviation.

pathologic response whereas pathologic regression grade 4 means completed pathologic response. Clinical response was based on comparison with pre-CCRT and post-CCRT MRI/CT scan and digital rectal examination. Completed clinical response means no tumor palpable and no lymphnodes via image examination whereas partial clinical response means decreasing size of tumor or decreasing amount of lymphnodes via image examination.

Three patients, who achieved complete clinical response via MRI scan and physical examination, received only local excision, so were excluded, leaving 19 patients in our study.

The method of statistical analysis for pathology response rates, curative resection rate, post-operative complication, was Fisher's exact test.

Results

Oxaliplatin based group & non-Oxaliplatin based group patients characteristics are shown in Table 1-1 & Table 1-2 separately. Most received total meso-rectal excision and almost of them had a protective ileostomy. In the study group, 18 patients (94.7%) had obvious tumor shrinkage size versus pre-CCRT confirmed by MRI/computer tomography and digital examination. Complete pathologic response was noted in 6 patients (31.6%) and partial pathologic response was noted in 13 patients (68.4%); overall pathologic response rate was 100% whereas complete pathologic response: 5 patients (11.6%), partial pathologic response: 29 patients (67.4%), no pathologic response: 9 patients (20.9%) while overall pathologic response rate was 79.1% in our previous non-oxaliplatin based group, as shown in Table 2-1 and Table 2-2. Curative resection rate (R0 resection rate) was higher in the Oxalipatin-based group (94.7%) than in the non-Oxaliplatin based group (90.7%), (p = 1.00), as shown in Table 3. The mean hospital stay was 9.0 days vs. 11.5 days; which was statistically significant (p = 0.003). Anastomosis leakage rate was obviously decreasing in the Oxaliplatin-based group, (5.3% vs. 27.5%, p = 0.075), as shown in Table 4.

In our series trial, CCRT related toxicity was mild,

Table 2-1. Pathologic response

	Oxaliplatin based		non-Oxaliplatin based		P-Value
	n	%	n	%	
CR+PR	19	100	34	79.1	0.047[f]
No rosponse	0	0	9	20.9	

[f] Fisher's exact test.

Table 2-2. Pathologic response

	Oxaliplatin based		non-Oxaliplatin based		P-Value
	n	%	n	%	
CR	6	31.6	5	11.6	0.031[p]
PR	13	68.4	29	67.4	
No rosponse	0	0	9	20.9	

[p] Peaeson Chi-square.
CR: complete response PR: partial reponse

Table 3. Circumferential margin status

	Oxaliplatin based		non-Oxaliplatin based		P-Value
	n	%	n	%	
CRM					1.000[f]
R0	18	94.7	39	90.7	
R1+R2	1	5.6	4	9.3	

[f] Fisher's exact test.

Table 4. Hospital course

	Oxaliplatin based		non-Oxaliplatin based		P-Value
	n	%	n	%	
Stay (day)	9.00 ± 3.96[a]		11.47 ± 4.75[a]		0.003[m]
leak					0.075[f]
+	1	5.3%	10	27.8%	
-	18	94.7%	26	72.2%	

[m] Mann-Whitney U test.
[f] Fisher's exact test.

as our previous control group,[1] as other reports.[13] Four patients (21%) developed mild GI tract discomforts and three patients (15.8%) developed grade I or II neutropenia. No patients developed grade III or IV neutropenia. There were no other acute severe toxic complications, which occurred during the period of CCRT, as shown in Table 5.

Discussion

Incomplete resection of rectal cancer eventually resulted in local recurrence and death. To improve this, Mile introduced abdominoperineal resection in the early 1900s.[4] With evolving instruments, a sphincter-saving procedure was performed in rectal cancer. Heald[8] developed total meso-rectal excision in 1982, which decreased local recurrence rate to less then 10%. In locally advanced rectal cancer, it remained a challenge until the early 1990s. Neo-adjuvant CCRT[11,12] offered the possibility of tumor shrinking, hence making curative resection possible with the findings of our previous paper.[1] Ralf-dieter Hofheinz.[14] enrolled 19 patients administered Cetuximab, Capecitabine, weekly Irinotecan and radiotherapy as neoadjuvant therapy for rectal cancer. Of the 19 patients, 18 underwent R0 resection (94.7%) and 1 underwent R1 resection. Nodal downstaging was detected in 12 of 18 patients (66.7%) and T stage was downstaged in 8 of 19 patients (42.1%). Complete tumor regression was found in 5 and microfoci (a few tumor cells scattered within fibrotic tissue) in 6 of the 19 patients, complete tumor regression: 26.3% and partial tumor regression: 31.6%. Claus Rodel.[15] collected 45 patients rolled in Cetuximab, Capecitabine, Oxaliplatin and radiotherapy as preoperative treatment for rectal cancer. Complete pathologic response was achieved in 4 (9%) of 45 patients. Seventeen patients (38%) showed good tumor regression (> 50% of the tumor mass). Moderate (n =12), minimal (n = 10) and no tumor regression (n = 2) were noted in 24 patients (53%). Comparing the diagnostic workup stage with the pathologic stage, tumor downstaging with respect to the T stage was observed in 21 (47%) of 45 patients and in 21 (58%) of 36 patients with respect to the N stage. Resection with negative circumferential margins at the primary tumor site was achieved in 42 (93%) of 45 patients. Marwan G. Fakih.[16] used 25 patients administered weekly intravenous Oxaliplatin combined with oral daily Capecitabine and radiotherapy with a biological correlatesin neoadjuvant treatment of rectal adenocarcinoma with an impressive complete pathologic response rate: 24%, and T downstaging: 44%. Due to impressive results noted in these three trials, we tried adding Oxaliplatin to our previous CCRT regimen, seeking improved results.

Table 5. CCRT related toxicity

Presentation	No. of patients.
Abdomen pain	1 (5.3%)
Nausea	2 (10.5%)
Vomitting	1 (5.3%)
Grade I neutropenia	2 (10.5%)
Grade II neutropenia	1 (5.3%)

In our series, 19 patients receiving Oxalipatin based Neo-adjuvant CCRT with overall pathologic response rate was 100% versus non-Oxaplatin based group: 79.1%, (p = 0.047), including pathologic complete response rate: 31.6% versus 11.6%, respectively (p = 0.019). Curative resection rate was 94.7% in the Oxaliplatin based group and 90.7% in the non-Oxalipatin based group, respectively, (p = 1.00). Although no statistical significance was noted, elevating tendency of R0 resection cannot be ignored. It is well known that by inducing tumor shrinkage leading to free curative resection, CCRT improves local control rate. Additional Oxaliplatin in CCRT increases pathologic response rate. The anastomotic leakage rate was (5.3%) which was better than the non-Oxaliplatin based group (27.8%). There is too much bias related to this result, such as patient baseline healthy conditions, surgeon technique and improvements in instru-

ments. The mean hospital stay was only 9.00 days, which was shorter than average: 11.47 days in our previous trial.

Our study had some significant limitations. The first limitation was a low rate of anastomosis leakage in the Oxaliplatin-based group, which allowed potential bias (may much matured operative technique induced, may obvious improvement in R/T (IMRT was applied in the study group, whereas conventional R/T in the control group). A second limitation is that case numbers were not big enough and observation was short-term. Long-term follow-up if local recurrence or distant metastasis occurs should be used for evaluating long-term benefits.

Conclusion

Oxaliplatin-based Neo-adjuvant CCRT increases the chance of tumor size shrinkage, a higher percentage of pathologic response rate (including complete and partial response) and a higher percentage of R0 resection without increasing complications or toxicity rates compared with a non-Oxaliplatin based Neo-adjuvant CCRT in Taichung Veterans General Hospital.

References

1. Twu CM, Wang HM, Chen JB. Neoadjuvant concurrent chemoradiotherapy in treating locally advanced rectal cancer. *J Chin Med Assoc* 2009;72(4):179-82.
2. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-51.
3. De Gramont A, Boni C, Navarro M, Tabernero J, Hickish T, Topham C. Oxaliplatin/5FU/ LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years. *J Clin Oncol* 2007;25:4007.
4. Miles WE. performing A method f abdomino-perineal excision for carcinoma of the rectum and the terminal portion of the pelvic colon. *Lancet* 1908;2:1812-3.
5. Miles WE. *Cancer of the Rectum*. London: Harrisons; 1926.
6. Surtees P, Ritchie JK, Phillips RK. High versus low ligation of the inferior mesenteric artery in rectal cancer. *Br J Surg* 1990;77:618-21.
7. Harnsberger JR, Vernava VM 3rd, Longo WE. Radical abdominopelvic lymphadenectomy: historic perspective and current role in the surgical management of rectal cancer. *Dis Colon Rectum* 1994;37:73-87.
8. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? *Br J Surg* 1982;69:613-6.
9. Kapiteijn E, Marijinen CAM, Colenbrander AC. *Eur J Surg Oncol* 1998;24:28-535.
10. Wolpin BM, Meyerhardt JA, Mamon HJ. Adjuvant treatment of colorectal cancer. *Cancer J Clin* 2007;57:168-85.
11. Marks G, Mohiuddin M, Rakinic J. New Hope and Promise for Sphincter Preservation in the Management of Cancer of the Rectum. *Seminars in Oncology* 1991;18:388-98.
12. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993;36:564-72.
13. Valenti V, Hernandez-Lizoain JL, Baixauli J, Pastor C, Aristu J, Diaz-Gonzalez J. Analysis of early postoperative morbidity among patients with rectal cancer treated with and without neoadjuvant chemoradiotherapy. *Ann. Surg Oncol* 2007;14: 1744-51.
14. Ralf-dieter H, Karoline H, Christoph W, Frederik W, Dietmar D. Phase I trial of cetuximab in combination with capecitabine, weekly irinotecan, and radiotherapy as neoadjuvant therapy for rectal cancer. *Int. J. Radiation Oncology Biol. Phys* 2006;66(5):1384-90.
15. Claus R, Dirk A, Matthias Hipp Y, Torsten L, Kathrin D, Igors I. Phase I-II trial of cetuximab, capecitabine, oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. *Int. J. Radiation Oncology Biol. Phys* 2008;70(4):1081-6.
16. Marwan FG, Bullarddunn K, Gary Y, Yang Y. Phase II study of weekly intravenous oxaliplatin combined with oral daily capecitabine and radiotherapy with biologic correlatesin neoadjuvant treatment of rectal adenocarcinoma. *Int. J. Radiation Oncology Biol. Phys* 2008;72:650-7.
17. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectum Disease* 1997;12:19-23.

原　著

局部侵犯性直腸癌之術前輔助性電化療，Oxaliplatin based

陳彥豪[1]　王輝明[1]　陳周斌[1]　趙德馨[1]　馬秀峰[1]　陳周誠[1]　蔣鋒帆[1]　涂嘉明[2]

[1]台中榮民總醫院　外科部　大腸直腸外科

[2]嘉義灣橋榮民醫院　外科部

目的　如何增加低位侵犯性直腸癌術後病理反應率及增加 R0 切除率，是外科手術之一大挑戰。本研究注重的是術前輔助性電化療額外加上 Oxaliplatin 在此類病患之效益及安全性。

方法　將本院 2008 年 1 月至 2008 年 11 月，22 位局部侵犯性直腸癌病患接受術前輔助性電化療，Oxaliplatin based，與本院之 2005 年 1 月至 2007 年 6 月，43 位局部侵犯性直腸癌接受術前輔助性電化療，Non-Oxaliplatin based 的病患進行比較。

結果　(1) Oxaliplatin based group 共有 19 位病患接受直腸癌根除性切除手術，19 位皆有病理反應，比率高達 100%，其中病理完全反應率高達 31.6%，與 Non-Oxaliplatin base group 相比有較高的病理反應率。(2) Oxaliplatin based group 其中 18 位有病理周圍邊緣無腫瘤侵犯之情形，R0 切除率爲 94.7%，與 Non-Oxaliplatin base group 相比有較高的 R0 切除率。(3) Oxaliplatin based group 總住院天數明顯下降，且有較低的併發症發生率。

結論　本研究發現於低位侵犯性直腸癌時，Oxaliplatin based 術前輔助性電化療，有較高的病理反應率，較高的 R0 切除率及較低的併發症發生率。

關鍵詞　局部侵犯性直腸癌、術前輔助性電化療、Oxaliplatin based、R0 切除率。