Original Article

Advantage of Oxaliplatin-Based Neoadjuvant Concurrent Chemo-Radiotherapy in Treating Locally Advanced Lower Rectal Cancer

Hung-Che Huang[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]
Ming-Cheng Chen[1]
Chia-Ming Twu[2]
Yen-Hao Chen[1]
[1]*Department of Surgery, Colorectal Section, Taichung Veterans General Hospital, Taichung*
[2]*Department of Surgery, Chiayi Veteran Hospital, Chiayi, Taiwan*

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

Background. Complete resection and postoperative treatment for lower advanced rectal cancer is problematic. Clearance of the tumor lesion presents a considerable challenge due to the difficult approachability, and thus the postoperative recurrence of the disease is relatively high. Neoadjuvant concurrent chemo-radiotherapy (CCRT), first described in 1990's, results in local control with a high percentage of R0 resection and pathologic response rate with comparable results in our previous study.[1] We compared Oxaliplatin-based CCRT with 5-FU alone CCRT and found the improved disease-free and overall survival in patients with stage III rectal cancer.[3,4] However, the duration of follow-up was short and the study population was small so in the current study we extended our previous research by collecting more patients' data, including a previous CCRT trial, and evaluated the advantages of Oxaliplatin-based CCRT versus the 5-FU CCRT over a one-year period.
Methods. From January 2004 to December 2009, (including our previous Oxlipaltin CCRT trial from January 2008 to December 2009, 19 cases),[2] 24 patients with locally advanced lower rectal cancer receiving Oxaliplatin-based neoadjuvant CCRT were enrolled for study group. From January 2005 to December 2009, 72 patients with locally advanced rectal cancer receiving 5-FU alone neoadjuvant CCRT were enrolled and comprised the control group. Factors including circumferential margin and pathologic response rate were evaluated.
Results. In the study group, the pathologic response rate was 95.6%, complete response rate was 39.1% and partial response rate was 56.5%. The Oxaliplatin group had a better pathologic response rate versus the 5-FU alone group (95.6% vs. 84.2%, $p < 0.0001$) with far superior results in complete pathologic response (39.1% vs. 7.0%) and a slightly improved circumferential margin rate (R0 resection 95.7% vs. 91.1%, $p = 0.857$). The Oxaliplatin group had better sphincter-saving ratio (91.7% vs. 68.1%, $p = 0.044$) and shorter stays (10.2 ± 4.9 vs.12.9 ± 9.0, $p = 0.028$). The study group had a tendency of lower local recurrence rate (0% vs. 3%, $p = 0.154$) and a higher survival than the control group (100% vs. 92%, $p = 0.395$) at the 24th month, although no statistically significance is available at the follow up timing.
Conclusion. Oxaliplatin-based neoadjuvant CCRT gives locally advanced lower rectal cancer patients more favorable results including higher tumor regression ratio, higher chance of sphincter-saving, shorter hospital stay without increasing complications.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2011;22:31-38*]

Received: June 8, 2010. Accepted: May 12, 2011.
Correspondence to: Dr. Hwei-Ming Wang, Division of Colorectal Surgery, Department of Surgery, Taichung Veterans General Hospital, No. 160, Section 3, Taichung Kong Road, Taichung, Taiwan. Tel: +886-4-2374-1207; Fax: +886-4-2350-0920; E-mail: whm@vghtc.gov.tw

Colorectal cancer is the most prevalent cancer in Taiwan with high morbidity and mortality rates in recent years. Advanced lower rectal cancer in particular is extremely problematic. Because of the anatomical limitation, complete resection and clearance of the lower rectal cancer is difficult, which leads to a high postoperative local recurrence rate and thus a low survival rate. Surgical therapy for lower rectal cancer has evolved since Ernest Miles first described the abdominoperineal resection in 1908.[5] By the 1920s, the operation had reduced the recurrence rate from almost 100% to approximately 30%,[6] thus ensuring this technique became the gold standard at that time while advocating extensive aggressive cancer therapy. However, the extreme devastating operation might lead to urinary, sexual, and gastrointestinal dysfunction which obviously affects patients' quality of life. Therefore, several modifications were attempted in order to reduce the extent and degree of destruction caused by the operation without sacrificing the local control and clearance of the cancer.[7,8] Anterior resection replaced abdominoperineal 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. In recent decades, improved suture material, including devices enabling low anastomosis, led to a shift toward sphincter-saving approaches with respect to cancer of the rectum. It was in this setting that total mesorectum excision (TME) was first described in 1982 by Heald and his colleagues,[8] which achieved the goals of preserving anus and sphincter, mostly complete cancer clearance and a recurrence rate less than 10%.[10] This advancement largely improved the postoperative quality of life of the diseased patients, and spared them the necessity of a permanent colostomy. Neoadjuvant concurrent chemo-radiotherapy (CCRT), which has been widely used in the last decade, provides local control for advanced rectal cancer at a higher percentage of R0 resection (margin clear under microscopic examination) and a lower recurrence rate.[11] 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.[3,4] Moreover, some published papers[15-17] have indicated that the addition of Oxaliplatin or Irontecan (Campto) into a pre-CCRT regimen might increase efficacy. In a previous paper[1] we demonstrated that neoadjuvant CCRT gave locally advanced lower rectal cancer patients more favorable results without increasing toxicity or complications. In another previously published study[2] we found that the use of Oxaliplatin-based neoadjuvant CCRT for treatment of low rectum cancer increased the chance of a higher percentage of pathologic response rate (including complete and partial response) and a slight increase in R0 resection rate without increasing complications or toxicity, when compared with 5-FU-based CCRT. However, the data showing the advantage of adding Oxaliplatin CCRT to 5-FU-based CCRT were limited due to the short duration of the study period which was two years. In this study, we hypothesised that addition of Oxaliplatin CCRT could provide long-term advantages on both tumor regression and local recurrence rate, with a longer disease-free period and better overall survival when compared with 5-FU-based CCRT so we extended the duration of the investigation by including data from patients treated prior to our previous study.

Method

From January 2004 to December 2009, data from 28 patients (including 19 cases from our previous Oxlipaltin-based CCRT trial from January 2008 to December 2009)[2] with locally advanced rectal cancer (diagnosed as fixed low rectal tumor by digital rectal exam or as T3-4 tumor by MRI/computer tomography. However, there had 5 patients in study group and 5 in control group who received preoperative CCRT for sphincter saving purpose but no definitive local advanced tumor.) receiving preoperative Oxaliplatin-based CCRT were collected and analyzed. Four patients in this group refused radical operation for personal reasons. Thus, some information, such as tumor regression grade and resection margins were unavailable and they were excluded from this group. From January 2005 to December 2009, 81 patients with locally advanced rectal cancer (diagnosed as fixed low rectal tumor by digital rectal exam or as T3-4 tumor by MRI/computer tomography) receiving

5-FU alone prior to CCRT were enrolled and comprised the control group.[1] In this group, 9 patients did not receive radical operation and were excluded. The general parameters, such as age, sex, preoperative lymph node staging, were non-significantly different between the two groups as can be seen in Table 1. The Oxaliplatin-based neoadjuvant 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, in addition to Oxaliplatin 85 mg/M^2, intravenously for two hours, on days 1-15-29, concurrent with radiotherapy (200 cGy per day, Monday to Friday for five weeks). The 5-FU alone prior to CCRT for locally advanced 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, concurrent with radiotherapy (200 cGy per day, Monday to Friday, for five weeks). Pathologic regression grading (PRG) was defined according to the tumor regression grading system proposed by 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 2-3 means partial pathologic response whereas pathologic regression grade 4 means complete pathologic response.

Statistical analysis

All statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). The Chi square test or Fisher's exact test and Yate's correction of contingency were used for categorical variables where appropriate. Mann-Whitney U test was used for comparison of patients' demographic data, tumor data, and hospital stay. Survival curves were estimated using Kaplan-Meier method. The survival curves were compared using log-rank test. A two-tailed p-value of < 0.05 was considered statistically significant for all tests.

Results

The characteristics of patients in the Oxaliplatin-based group and 5-FU alone group are shown in Table 1. The general parameters, such as age, gender, preoperative lymph node staging, and so on, of both groups were significantly different.

In the Oxaliplatin-based group, 22 patients (91.7%) received total mesorectum excision (TME) with/without protective loop ileostomy and only two patients (8.3%) received abdominoperineal resection (APR). In the 5-FU alone group, 49 patients (68.1%) received TME, 22 patients (30.6%) received APR, and one patient (1.4%) received Hartmann's operation. The APR ratio in the Oxaliplatin-based group was lower compared with that in the 5FU alone group (p = 0.073). However, there was a greater possibility of laparoscopic operation and a higher percentage of sphincter-saving resection in the study group compared with the control group (Table 2).

As there was no description of tumor regression grade in the earlier pathology report, regression grade data were only available in 23 patients in the study group and in 57 patients in the control group. However, the regression data shown in Table 2 still reveal some interesting findings. In the study group, complete pathologic response was noted in 9 patients (Regression grade 4; 39.1%) and partial pathologic response was noted in 13 patients (Regression grade

Table 1. Demographics

Radiosensitizer	Oxaliplatin (n = 24)	5-FU (n = 72)	p-value
Mean Age (SD)	57.9 (10.2)	56.3 (14.5)	0.591[b]
Gender M/F	14/10	39/33	0.906[d]
DM	2 (8.3%)	9 (12.5%)	0.725[a]
HTN	3 (12.5%)	15 (20.8%)	0.548[a]
Smoking	3 (12.5%)	15 (20.8%)	0.548[a]
Drinking	1 (4.2%)	4 (5.6%)	1.000[a]
CAD	0	4 (5.6%)	0.569[a]
Pelvic LN[%]	3 (12.5%)	3 (4.2%)	0.163[a]
Mesorectal LN[&]	3 (12.5%)	5 (6.9%)	0.408[a]
Pre-CCRT CEA	10.0 (16.7)	22.0 (25.8)	0.081[b]
Post-CCRT CEA	3.7 (2.7)	7.8 (21.7)	0.785[b]

a. Fisher's exact test; b. Mann-Whitney U test; c. Pearson Chi-Square test; d. Yate's correction of contingency.
%: presence of mesorectal lymph node metastasis on pre-CCRT abdominal computed tomography.
&: Presence of pelic lymph node metastasis on pre-CCRT abdominal computed tomography.

Table 2. Procedures of radical excision after CCRT

	Oxaliplatin (n = 24)	5-FU (n = 72)	*p*-value
TME	22 (91.7%)	49 (68.1%)	
APR	2 (8.3%)	22 (30.6%)	0.073[a]
Hartmann's procedure	0	1 (1.4%)	
Sphincter-saving	22 (91.7%)	49 (68.1%)	0.044[b]
Laparoscopy	21 (87.5%)	43 (59.7%)	0.024[b]

a. Pearson Chi-Square test; b. Yate's correction of contingency.
TME = Total Mesorectum Excision.
APR = Abdominal Perineal Resection.

2-3; 56.5%) and only 1 patient was assigned to the poor regression subgroup; overall pathologic response rate was at least 95.6%. In the control group, complete pathologic response was found in 4 patients (7%), partial pathologic response in 44 patients (77.2%), and no pathologic response was found in 9 patients (15.8%), while overall pathologic response rate was 84.2%, as shown in Table 3. Data of circumferential margin were only available in some cases; we defined that no tumor cell presents within 1mm of circumferential margin as R0 resection. Twenty three patients in the study group had a circumferential margin record and 22 patients (95.7%) reached R0 resection compared with 41 of 45 patients (91.1%) in the control group ($p = 0.857$) (Table 3).

Table 4 shows the postoperative pathologic stage of T. In our earlier pathology report integrated tumor staging was not recorded. Thus, only data from 48 patients in the control group, (i.e., those who had an integrated tumor staging record) are shown in this table. The table shows tumor shrinkage and the T down-staging. In the study group, four patients with clinical T4 stage tumor were down-staged to pT3 (100%). The same result was found in the control group; in four patients with clinical T4 tumor 3 were down-staged to pT3 and one patient (100%) was down-staged to pT1. In the study group, among the 15 patients with clinical T3 stage tumor, six patients were down-staged to pT2, one patient was down-staged to pT1, and three patients were down-staged to pT0 (down-stage rate 66.7%). However, the percentage of patients who were down-staged for clinical T3 tumor in the control group was 33.3% ($p = 0.035$). Overall, 18 of 24 patients (75%) were down-staged in the study group compared with 18 of 48 patients (37.5%), $p = 0.006$ in the control group.

The postoperative hospital stay in the Oxliplatin-based CCRT group was significantly shorter, 10.2 ± 4.9 days compared with 12.9 ± 9.0 days ($p = 0.028$) in

Table 4.1. Tumor down-staging

	Oxaliplatin (n = 24)					5-Fu (n = 48)				
	n	pT4	pT3	pT2	pT1	pT0	n	pT4	pT3	pT2	pT1	pT0
cT4	4		4				4		3	0	1	
cT3	15		5	6	1	3	39		26	7	2	4
cT2	5			1	1	3	5			4	1	
cT1	0											

Table 4.2. Ratio of tumor down-staging

	Oxaliplatin	5-Fu	*p*-value
cT4	4/4 (100%)	4/4 (100%)	N/A
cT3	10/15 (66.7%)	13/39 (33.3%)	0.035[a]
cT2	4/5 (80%)	1/5 (20%)	0.206[a]
cT1	0	0	N/A
Total	18/24 (75%)	18/48 (37.5%)	0.006[b]

a. Fisher's exact test; b. Yate's correction of contingency.
* in 5-Fu group, clinical staging and pathology staging was available in only 48 of 81 cases. Thus, comparison of down-staging was possible in 48 cases only.

Table 3. Clinical features, histopathology features

Radiosensitizer	Oxaliplatin (n = 24)	5-FU (n = 72)	*p*-value
Mean distance from anal verge (CM) (SD)	5.2 (1.3)	5.0 (1.6)	0.596[b]
Regression grade available	23	57	
Regression grade 4	9 (39.1%)	4 (7.0%)	< 0.001[c]
Regression grade 2-3	13 (56.5%)	44 (77.2%)	
Regression grade 0-1	1 (4.3%)	9 (15.8%)	
Pathology complete response (Regression grade 4)	9 (39.1%)	4 (7.0%)	0.001[a]
Distal cut end (cm) (SD)	2.4 (1.2)	2.5 (1.5)	0.973[b]
Margin available	23	45	
Circumferential margin (mm) (SD)	6.6 (4.6)	7.7 (4.3)	0.391[b]
R0 resection	22/23 (95.7%)	41/45 (91.1%)	0.851[d]

a. Fisher's exact test; b. Mann-Whitney U test; c. Pearson Chi-Square test; d. Yate's correction of contingency.

the 5-FU alone group. The postoperative morbidity shown in Table 5 included wound infection, pelvic abscess, postoperative ileus and anastomosis leakage. There was no significant increase in morbidity in the Oxaliplatin-based CCRT group. The toxicity of these two groups is also shown in Table 5, which includes skin toxicity, radiation colitis, and hematological adverse effects. There were no significant differences between these two groups.

The survival rates in the two groups are shown in Figure 1. The Oxaliplatin-based CCRT group was followed up for about 24 months and the survival rate in this group was 100% compared with 92% in the 5-FU alone group in the same follow up period ($p = 0.395$), although this was not a statistically significant difference. Local recurrence rate in the Oxaliplatin-based group was 0% at the 24th month, and 3% in the 5-FU alone group at the same time point and 9% at the 60th month ($p = 0.154$). Although these values were not statistically significant, there was a tendency for a lower local recurrence rate in the study group (Figure 2).

Discussion

Incomplete resection of advanced lower rectal cancer eventually results in local recurrence and death. In order to improve recurrence and mortality rates, Miles introduced the abdominoperineal resection in the early 1900s.[5] With evolving instruments, a sphincter-saving procedure was later developed rectal cancer. Heald[9] developed total meso-rectal excision in 1982, which decreased the local recurrence rate to less than 10%. Treatment options for locally advanced rectal cancer remained a considerable challenge until the early 1990s when neoadjuvant CCRT[12,13] was de-

Table 5. Hospital stay, operative complications and toxicities of radiotherapy

Radiosensitizer	Oxaliplatin + 5-FU (n = 24)	5-FU only (n = 72)	*p*-value
Hospital stay (SD)	10.2 (4.9)	12.9 (9.0)	0.028[b]
Wound infection	0/24	4/72 (5.6%)	0.555[c]
Pelvic abscess	0/24	3/72 (4.2%)	0.735[c]
Post-op ileus	1/24 (4.2%)	4/72 (5.6%)	1.000[c]
Anastomosis leakage	1/22 (4.5%)	9/49 (18.4%)	0.158[c]
Perineal wound poor healing	0/2	1/22 (4.5%)	1.000[c]
Skin toxicity	1 (4.2%)	2 (2.8%)	1.000[a]
Radiation colitis	14 (58.3%)	38 (52.8%)	0.813[d]
Hematology Adverse effect*	1 (4.2%)	14 (19.4%)	0.105[a]

a. Yate's correction of contingency; b. Mann-Whitney U test; c. Fisher's exact test; *: neutropenia > Gr III.

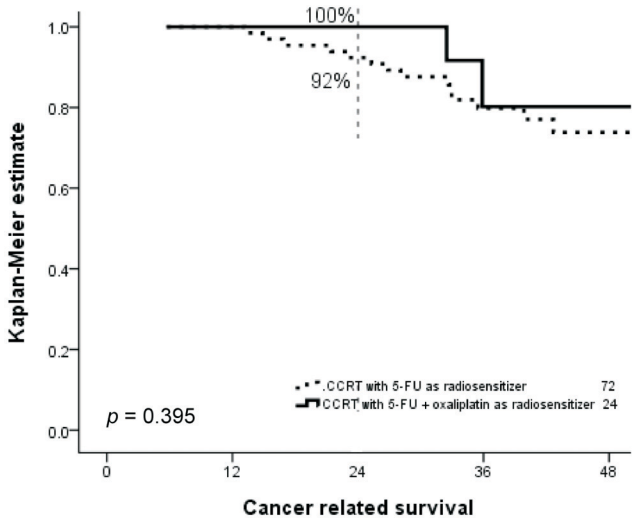

Fig. 1. Cancer related survival.

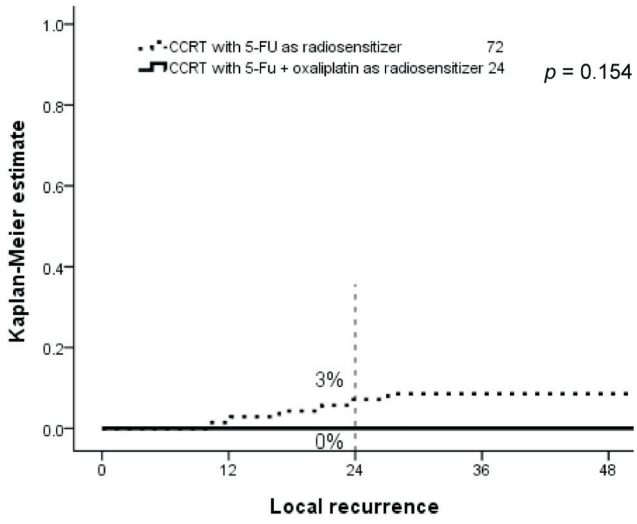

Fig. 2. Local recurrence rate.

veloped, which offered the possibility of tumor shrinking, and hence made curative resection possible as described in our previous paper.[1] Ralf-dieter Hofheinz.[15] enrolled 19 patients who received 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 down-staged in 8 of 19 patients (42.1%). Complete tumor regression was found in 5 and microfoci (a few tumor cells scattered within fibrotic tissue) were noted in 6 of the 19 patients, with complete tumor regression in 26.3% of the patients, and partial tumor regression in 31.6%.

Claus Rodel[16] assessed 45 patients who received Cetuximab, Capecitabine, Oxaliplatin and radiotherapy as preoperative treatment for rectal cancer. Complete pathologic response was achieved in 4 of 45 patients (9%). 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 down-staging with respect to the T stage was observed in 21 of 45 patients (47%) and in 21 of 36 patients with respect to the N stage (58%). Resection with negative circumferential margins at the primary tumor site was achieved in 42 (93%) of 45 patients.

Due to the impressive results obtained in these two trials, we added Oxaliplatin to our previous CCRT regimen, seeking improved results. Our previous study compared Oxaliplatin and CCRT with 5-FU alone followed by CCRT. Then in the current study we enrolled more patients in both groups in the following year and included the data dating back to 2004 from the previous solitary clinical trial in order to better determine the long-term effects.

In our series, 24 patients received Oxaliplatin in addition to CCRT and 72 patients received 5-FU alone followed by CCRT. The tumor regression rate of the study group was 95.6%, compared with 84.2% in the control group. Importantly, the regression grade 4 rate increased in the study group up to 39.1%, compared with 7.0% in the control group.

Regarding the operation procedure, the APR rate in the study group was significantly lower than in the control group (8.3% versus 30.6%), and the laparoscopic procedure rate was significantly higher than in the control group (87.5% versus 59.7%). This implies that the clinical down-staging of the local advanced tumor led to a higher probability of sphincter preservation and allowed for a less challenging operation. It also likely accounted for the shorter hospital stay and higher R0 resection rate.

With respect to the long term survival and local recurrence rate, although no statistical significance was found between the two groups, the statistical curves appeared to separate gradually. The survival rate in the study group at the 24th month was 100%, which was better than the rate of 92% found in the control group, The local recurrence rate showed a similar trend with a lower recurrence rate in the study group than in the control group. This indicates that the addition of Oxaliplatin resulted in better survival and lower local recurrence compared with the 5-FU alone group, although no statistical significance was found. Comparing the two groups, Oxalipatin group had better pathology response and downstage of the advanced lower rectal cancer, this may account for better complete resection rate (R0 resection). We know incomplete resection eventually lead to local recurrence and influence survival. Therefore we can found the advantage of Oxaliplatin based neoadjuvant CCRT, trend of lower local recurrence and better survival which come from better tumor regression and downstage thus higher complete resection.

Our study had some significant limitations. The first limitation was a low rate of anastomosis leakage in the Oxaliplatin group, which may have resulted in potential bias (a more mature operative technique was adopted in the study group, yielding an obvious improvement in R/T; IMRT was applied in the study group, whereas conventional R/T was used in the control group). A second limitation was that the case number was low and the observation period was not long enough to obtain a significant result between the two groups. Further follow-up to investigate improvements in long-term survival, local recurrence and distant metastasis are recommended.

Conclusion

Oxaliplatin-based neoadjuvant CCRT increases the chance of tumor regression, a higher percentage of pathologic response (including complete and partial response), higher percentage of R0 resection, higher sphincter-saving rate, shorter hospital stays, without increasing complications or toxicity, trend of better survival and local recurrence rate when compared with a non-Oxaliplatin-based neoadjuvant 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;72:179-82.
2. Chen YH, Wang HM, Chen JB. Oxaliplatin-based neoadjuvant concurrent chemo-radiotherapy in locally advanced lower rectal cancer. *J Soc Colon Rectal Surgeon* 2010;21: 17-22.
3. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-51.
4. De Gramont A, Boni C, Navarro M, et al. 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.
5. Miles WE. Performing a method f abdomino-perineal excision for carcinoma of the rectum and the terminal portion of the pelvic colon. *Lancet* 1908;ii:1812-3.
6. Miles WE. Cancer of the rectum. London: Harrisons; 1926.
7. 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.
8. 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.
9. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? *Br J Surg* 1982;69:613-6.
10. Kapiteijn E, Marijinen CAM, Colenbrander AC. *Eur J Surg Oncol* 1998;24:28-535.
11. Wolpin BM, Meyerhardt JA, Mamon HJ. Adjuvant treatment of colorectal cancer. *Cancer J Clin* 2007;57:168-85.
12. 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.
13. 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.
14. Valenti V, Hernandez-Lizoain JL, Baixauli J, et al. Analysis of early postoperative morbidity among patients with rectal cancer treated with and without neoadjuvant chemoradiotherapy. *Ann Surg Oncol* 2007:14:1744-51.
15. Ralf-dieter Hofheinz, Karoline Horisberger, Christoph Woernle, et al. 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;66:1384-90.
16. Rodel C, Arnold D, Hipp YM, et al. Phase I-II trial of cetuximab, capecitabine, oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. *Int J Radiation Oncology Biol Phys* 2008;70:1081-6.
17. Fakih MG, Bullarddunn K, Yang YGY, et al. 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.
18. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectum Disease* 1997;12:19-23.

原　著

使用 Oxaliplatin 為基礎的術前同步化放療於治療低位進行期直腸癌的優勢

黃宏哲[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]　陳明正[1]　涂嘉明[2]　陳彥豪[1]

[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

背景　低位進行期直腸癌不論是在完全切除或是術後追蹤治療上都充滿了困擾。因為解剖學上的限制，要將低位進行期直腸癌完全切除乾淨非常困難，也因此增加術後復發的機會。在 1990 年代開始有人提出術前的同步化放療療法，用以增加疾病的局部控制並且提升完全切除的機會與病理縮減反應的比率，這與我們先前發表過的研究結果相符。之後我們再提出單純使用 5-FU 的術前同步化放療與追加使用 Oxaliplatin 的術前同步化放療的比較，歸結出追加 Oxaliplatin 的同步化放療比單純使用 5-FU 的同步化放療似乎有助於延後疾病的復發和延長生存比率的傾向。然而當時的研究不論追蹤期間與病人數量皆不足。因此我們擴展這項研究，收集從 2004 年開始至今的，數位接受 Oxaliplatin 同步化放療的病人資料，得到較長的追蹤結果，期望能得到更強的證據，證明追加 Oxaliplatin 的同步化放療比單純用 5-FU 的治療能得到更多的好處。

方法　我們收集從 2004 年 1 月到 2009 年 12 月之間，使用追加 Oxaliplatin 的同步化放療的 24 位低位進行期直腸癌病人資料，其中包括先前本科發表的從 2008 年開始的追加 Oxaliplatin 的同步化放療 19 位病人的資料，作為研究組。收集 2005 年 1 月到 2009 年 12 月，單純使用 5-FU 的術前同步化放療的 72 位病人為控制組，比較兩組的差異性，包括切除標本的腫瘤週圍邊界與病理反應程度都列入比較。

結果　在研究組中，病理反應比率達 95.6%，其中完全反應比率可達 39.1%，部分反應比率為 56.5%。追加 Oxaliplatin 的組別和單純使用 5-FU 的組別相比，有較佳的病理反應比率 (95.6% vs. 84.2%, $p < 0.0001$)，尤其是完全反應的比率比較 (39.1% vs. 7.0%) 與完全切除的比率 (95.7% vs. 91.1%, $p = 0.851$)。追加 Oxaliplatin 的組別術後有較短的住院天數，在同樣第 24 個月的追蹤期，似乎有較高的生存率，和較低的復發率傾向。

結論　追加使用 Oxaliplatin 的術前同步化放療治療低位進行期直腸癌，對病患能提供較好的預後：包括較佳腫瘤縮減反應，較高保留肛門擴約肌的機會，較短的住院天數，似乎也能減少局部復發比率與延長存活期，並且不增加額外的併發症。

關鍵詞　益樂鉑錠、術前同步化放療、直腸癌。