*Case Analysis*

# Impact of Pre-Operative Chemoradiotherapy on cT3N0M0 Middle and Low Rectal Cancer

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***Key Words***
Concurrent ChemoRadioTherapy (CCRT);
Magnetic Resonance Imaging (MRI);
Computed Tomography (CT)

***Purpose.*** To evaluate the oncological benefit of neoadjuvant concurrent Chemo-RadioTherapy (CCRT) for cT3N0M0 rectal cancer.
***Materials and Method.*** Between July 2000, and December 2004, 103 patients of middle and low rectal cancer with primary cT3N0M0 were enrolled. Of them, 37 patients were staged by magnetic resonance imaging (MRI), and 66 by computed tomography (CT); 80 patients did not receive pre-operative concurrent Chemo-RadioTherapy (CCRT) and 23 did. Radical resections were performed as the protocol. The oncological results including survival, local and distant metastasis rates were analyzed.
***Results.*** For the concurrent Chemo-RadioTherapy (CCRT) group, the complete response rate was 34.8% and the down staging rate was 73.9%. There was no significant difference in survival analysis between the two groups (OS: 91.3% vs. 82.1%; DFS: 86.4% vs. 79.5%; CSS: 91.3% vs. 91.0%), neither in local (10% vs. 4.3%) nor distant control (23.8% vs. 17.4%).
***Conclusion.*** Pre-operative concurrent Chemo-RadioTherapy (CCRT) might not provide better local control or survival benefit for cT3N0M0 middle and low rectal cancer.
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Early rectal cancer can be successfully managed with surgical resection.[1] However, for advanced disease (T3,4 or N+) treated with surgery alone, the reported local recurrent rate was about 10~30%.[2] (more complicated lymphatic and venous drainage system of the rectum).[3]

Pre-operative chemoradiotherapy (CCRT) followed by radical resection can significantly reduce the local recurrence rate of advanced rectal cancer.[4] However, the benefit of CCRT or radiotherapy alone on the survival rate is still controversial.[5-7]

The disadvantages of pre-operative CCRT are mainly anastomotic leakage or stenosis; while its advantage for those who have middle or low rectal cancer with clinical cT3N0M0 remains undetermined. With advances in total mesorectal excision (TME), surgical technique (R0 resection), and oncological managements (chemotherapy), whether pre-operative CCRT is necessary for those who have cT3N0M0 becomes uncertain.

The standard protocol of pre-operative CCRT in our hospital has been established since 2000.[8] Total mesorectal excision (TME) was performed routinely in operation of middle and low rectal cancer in our hospital.

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The aim of this study was to evaluate whether cT3N0M0 patients receiving pre-operative CCRT followed by radical surgery had better prognosis or more complications (anastomotic leakage or stenosis) as compared with those without CCRT.

In this article, we will present the complications, recurrence, and survival in patients with and without pre-operative CCRT after 5-year long-term follow-up.

## Patients

Patients with primary rectal adenocarcinoma pathologically confirmed were retrospectively enrolled. To qualify for enrollment, the primary tumor must be clinical T3 according to AJCC staging system and lower seated (< 10 cm from anal verge). The tumor should be treatable by conventional RT treatment portals without evidence of distant metastases. Other inclusion criteria were no prior chemotherapy or RT; no other malignancy; absolute granulocyte count > 1,500/mm$^3$; platelet count > 100,000/mm$^3$; bilirubin, transaminases, and creatinine levels < 1.5-fold of the upper normal limit. Pre-treatment evaluation included a complete history and physical examination, complete blood count, liver function tests, and carcinoembryonic antigen (CEA) level determination. Computer tomography (CT) scan or magnetic resonance imaging (MRI) and proctoscopy were employed to evaluate the primary disease.[9-11] Tumor-involved lymph nodes were identified by size criteria. Nodes with diameter exceeding 5 mm in diameter were reported as nodal metastases.[12] Chest X-ray, abdominal ultrasonography, and whole body bone scan were performed for systemic evaluation. Informed consent was obtained from all patients.

## Methods

### Treatment protocol

Radiation therapy was administered with a linear accelerator producing 10 MV X-rays. In cases with mid- to upper rectal lesions (≥ 6 cm from anal verge), the entire pelvis was treated with AP-PA plus bilateral portals daily. The superior margin was at the L5-S1 junction or higher for the sigmoid-rectal junction tumor; the lateral margins were 1.5 cm lateral to the widest bony margin of the true pelvic sidewall. The inferior margin was at least 3 cm below the primary tumor or at the inferior aspect of the obturator foramina, depending on which was the most inferior. The anterior margin was located behind the symphysis pubis. The posterior margin was 0.5 cm behind the posterior surface of the sacrum and coccyx. For lower-seated (< 6 cm from the anal verge) rectal tumors, the three-field (patient's posterior and bilateral) technique was used. In order to exclude the small bowel from the radiation volume, patients were routinely treated in a prone position with a homemade "belly board." The upper margins of the radiation fields were coincided with the lower margin of the opening (26 × 28 cm$^2$) of the board. Radiation therapy was delivered once per day with a 2.25-Gy fraction, 5 days per week. Total dose was 45 Gy over 4 weeks.[8] Concurrent chemotherapy was administered from days 1 to 28, during the entire course of RT. The dose of UFUR (TTY Biopharm, Taipei, Taiwan) was initially 200 mg/m2/day. The total daily dose was divided into three doses per day. The dose of LV (Wyeth Lederle Laboratories, Taipei, Taiwan) was 45 mg/day divided in three doses. The oral chemotherapy was continued after RT with a dose of 250 mg/m2/day in another 28-day cycle on days 36-63.[8] Surgical resection was scheduled at 6-8 weeks after completion of RT. Total mesorectal excision (TME) was performed.[13] Distal safety margin rule of 2 cm was followed, and tumor-free margin was obtained for every potentially curative operation. Reversal of colostomy or ileostomy was performed about 3 to 6 months after radical surgery. The patients were followed every 3 months post-operatively during the first 2 years and every 6 months afterwards (CEA, abdominal sonography and abdominal CT) Pathological staging was available in these patients and compared with the initial clinical stages.

### Statistical analysis

The numeric data such as difference in age of onset and distance from anal verge to tumor were compared with independent-samples t-test. The category

data such as prognostic factor, complication, and rate of recurrence were compared using chi-square test with Yates' correction. The primary end point and survivals were analyzed using Kaplan-Meier method with log-rank test. Overall survival was calculated from the date of enrolment till to death. Disease-free survival was calculated from the date of surgery till failure in treatment. Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS version 16.0, Chicago, IL). Results with $p$-values < 0.05 were considered significant.

## Results

A total of 103 patients diagnosed with middle and low rectal adenocarcinoma (less than 10 cm from anal verge) were enrolled for analysis. Among them, 80 patients with cT3N0 rectal cancer who did not receive pre-operative CCRT and 23 did. General characteristics of all patients studied were summarized in Table 1. Compared with patients without pre-operative CCRT, those with pre-operative CCRT had a higher percentage of sphincter preservation surgery (LAR). However, the difference did not reach statistical significance ($p = 0.660$).

Table 2 shows the final pathological stages of the 80 patients without pre-operative CCRT. Compared with that of the clinical stage, the accuracy of pre-operative staging by image was 58.75% (47/80). The over staging rate was 28.75% (23/80) while the under staging rate was 12.50% (10/80).

Table 3 shows the pre-treatment and final pathological T-stage results of the 23 patients with pre-operative CCRT. Among them, 8 patients had no residual tumor found in the resected specimen. The pathological complete response (pCR) rate was 34.78% (17/23). The down staging (DS) rate for the invasion

**Table 1. Patients and tumor characteristics and type of operation in patients with and without pre-op CCRT**

| Case No. | Pre-op CCRT | | p value |
|---|---|---|---|
| | No<br>80 | Yes<br>23 | |
| Age/year/mean ± S.D.[a] | 69.86 ± 10.45 | 67.27 ± 12.14 | 0.233 |
| Tumor location/cm/ mean ± S.D. (from anal verge) | 6.21 ± 2.10 | 5.13 ± 1.98 | 0.577 |
| | Case No. (%) | Case No. (%) | |
| Pre-op CEA (ng/ml) | | | 0.227 |
| ≥ 5 | 41 (51.9) | 8 (34.8) | |
| < 5 | 38 (48.1) | 15 (65.2) | |
| Pre-op Albumin (g/dl) | | | 0.903 |
| ≥ 3.5 | 41 (51.3) | 14 (60.9) | |
| < 3.5 | 39 (48.7) | 9 (39.1) | |
| Surgery | | | 0.660 |
| APR[a] | 27 (33.8) | 6 (26.1) | |
| LAR[a] | 53 (66.2) | 17 (73.9) | |
| Follow-up | | | |
| Month, median (range) | 60.2 (7.8~99.5) | 57.1 (8.83~95.9) | 0.816 |

[a] S.D.: standard deviation; APR: Abdominoperineal resection; LAR: Low anterior resection.

**Table 2. Over/under staging result in 80 patients without pre-operative chemoradiotherapy**

| Clinical stage | Pathological stage | | | | Over vs. under staging (%) |
|---|---|---|---|---|---|
| T3 | PT2N0 | PT3N0 | PT3N1 | PT4N0 | 22/80 (27.5) |
| Case No. 80 | 22 | 47[a] | 10 | 1 | 11/80 (13.6) |

[a] Accuracy of pre-op staging by image: 47/80 (58.8%).
[a] Accuracy of MRI: 19/28 (67.9 %), CT: 28/52 (53.8%), $p = 0.329$.

of primary tumor was 73.91% (17/23).

Table 4 shows the post-operative complications of the 70 patients with sphincter preservation surgery (LAR). Among the CCRT group, 17 patients received a sphincter preservation surgery (LAR) (73.9%, 17/23), with 14 of them having colostomy or ileostomy. Among the non-CCRT group, 53 patients received a sphincter preservation surgery (LAR) (66.2%, 53/80), with 21 of them having colostomy or ileostomy but not the remaining 32. Five patients in the non-CCRT group experienced anastomotic leakage, with one having fistula formation and two developing anastomotic bleeding. However, the number of patients developing complications did not reach statistical significance.

Table 5 shows the percentage of local or distal recurrence rate in patients with and without pre-operative CCRT. As can be seen, the local recurrence rate was 4.3% in patients with pre-operative CCRT, which was lower than 10.0% in those without pre-operative CCRT ($p = 0.398$). The incidence of total recurrence among patients with and without pre-operative CCRT were similar (21.7% vs. 27.5%, $p = 0.776$). No difference of statistical significance was observed.

The 5-year overall survival (OS) rate was 91.3% for patients with pre-operative CCRT, and 82.1% for those without (Fig. 1), but the difference did not reach statistical significance ($p = 0.326$). The 5-year disease free survival (DFS) rate was 86.4% for patients with pre-operative CCRT, and 79.5% for those without (Fig. 2), with difference also not of statistical significance ($p = 0.698$). The 5-year cancer specific survival (CCS) rate was 91.3% for patients with pre-operative CCRT, and 91.0% for those without (Fig. 3), and the difference is still of no statistical significance ($p = 0.964$).

**Table 3. Down staging result in 23 patients with pre-operative chemoradiotherapy**

| Clinical stage | Pathological stage | | | | Down staging (%) |
|---|---|---|---|---|---|
| T3 | yPT0 | yPT1 | yPT2 | yPT3 | |
| Case No.23 | 8[a] | 1 | 8 | 6 | 17/23 (73.91) |

[a] Complete response: 8/23 (34.8%).

**Table 4. Post-operative complication in 70 patients with LAR**

| Case No. | Pre-op CCRT | | *p* |
|---|---|---|---|
| | No<br>53[a] | Yes<br>17[b] | |
| | Case No. (%) | Case No. (%) | |
| Anastomotic leakage | 5[a] (9.4) | 0[b] | 0.189 |
| Fistula formation | 1 (1.9) | 0 (0) | 0.568 |
| Anastomotic stenosis | 0 (0) | 0 (0) | - |
| Anastomitic bleeding | 2 (3.8) | 0 (0) | 0.416 |

[a] Colostomy (13, 1), ileostomy (8, 0), and without diversion (32, 4).
[b] Colostomy (13, 0), ileostomy (1, 0), and without diversion (3, 0).

## Discussion

Pre-operative CCRT followed by resection of T3N0 rectal cancer is recommended in order to reduce the incidence of local recurrence and improve survival. However, recent experience with rectal cancer

**Table 5. Local recurrence or distal metastasis in patients with and without pre-op CCRT**

| Case No. | Pre-op CCRT | | *p* |
|---|---|---|---|
| | No<br>80 | Yes<br>23 | |
| | Case No. (%) | Case No. (%) | |
| Total recurrence | 22 (27.5) | 5 (21.7) | 0.776 |
| Local recurrence | 8 (10) | 1 (4.3) | 0.398 |
| Distant metastasis | | | |
| Liver | 7 (8.8) | 0 (0) | 0.142 |
| Lung | 12 (15.0) | 4 (17.4) | 0.780 |

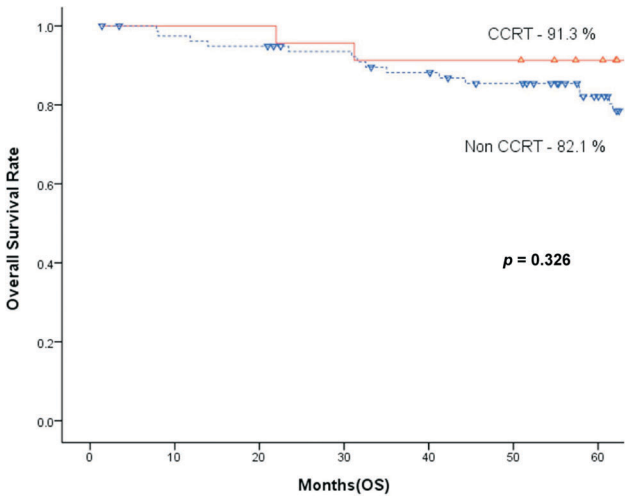


**Fig. 1.** Overall survival rate in patients with and without pre-op CCRT.

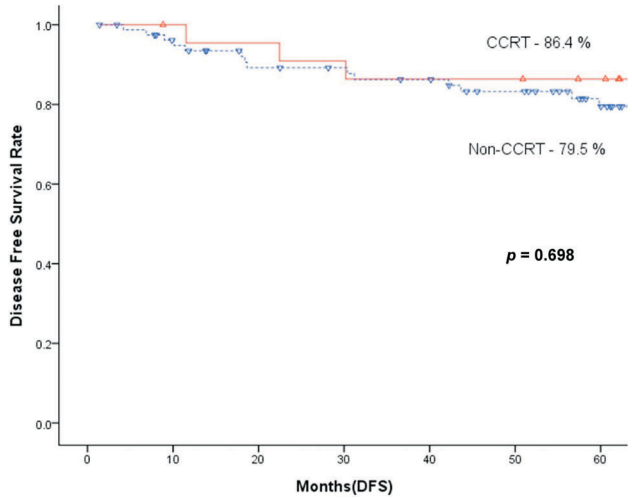


**Fig. 2.** Disease free survival rate in patients with and without pre-op CCRT.

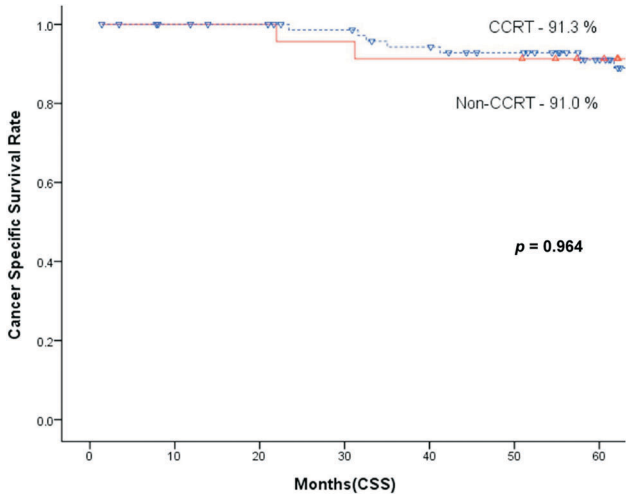


**Fig. 3.** Cancer specific survival rate in patients with and without pre-op CCRT.

resection utilizing sharp dissection and total mesorectal excision (TME) has resulted in a reduction in local recurrence rates to as low as 5% without adjuvant treatment.[14] Therefore, in selected patients with T3N0M0 rectal cancer, the routine use of neo-adjuvant therapy for local control is not justified.

In this study, for primary cT3N0M0 middle and low rectal cancer, CCRT has achieved complete response rate of 34.8%, and down staging rate of 73.9%. However, it does not have significantly better survival benefit, local or distant control, compared with surgery alone.

Fortunately, CCRT caused little complication in this series. The reason may be that 14 patients (14/23) of those with pre-operative CCRT had diversion with colostomy or ileostomy post-operatively. None of them experienced anastomotic leakage, fistula formation, anastomotic stenosis, or anastomotic bleeding. The tumor location did not reach statistical significance between the two groups (Table 1). One patient in the non-CCRT group experienced fistula formation and two developing anastomotic bleeding. It may be caused by machenical problems of autosuture instruments (surgical stapling). However, the number of patients developing complications did not reach statistical significance. Among the 35 patients having colostomy or ileostomy, they received reversal of enterostomy without complications 3 to 6 months after radical surgery.

For a better understanding, a prospective randomized study with a larger number of cases is needed. Furthermore, the accuracy of pre-operative image staging needs to be improved. We selected 47 patients from the non-CCRT group whose clinical stages corresponded with their pathological stages after surgery. This sub-group was compared with those receiving pre-operative CCRT, that is, these 47 patients with pT3N0M0 rectal cancer who did not receive pre-operative CCRT were compared with the 23 patients who did. All results obtained were similar to previous ones.

The percentage of local recurrence rate was 4.3% in patients with pre-operative CCRT, which was lower then 10.6% in those without pre-operative CCRT ($p = 0.377$). The incidence of total recurrence among patients with and without pre-operative CCRT (21.7% vs 21.3%, $p = 0.965$) were similar. No statistically significant difference in local or total recurrence rate was observed.

The 5-year overall survival (OS) rate was 87.0% for patients with pre-operative CCRT, and 85.1% for those without. The 5-year disease free survival (DFS) rate was 83.0% for patients with pre-operative CCRT, and 82.6% for those without. Both rates were similar.

Kim et al. indicated that patients with T3,4N0 rectal cancer who underwent proctectomy with complete mesorectal excision yielded a 4.2 percent local recurrence rate without the need for CCRT. Therefore, the potential risks, costs, and benefits of adjuvant pelvic CCRT for rectal cancer must be considered.[15] Law et

al. reported that 224 patients (141 men), from August 1993 to December 2002, with Stage II rectal cancer underwent curative surgery without adjuvant radiation and a low local recurrence rate was found.[16] Lai et al. also indicated that patients with stage II lesions have relatively low risks of local recurrence when treated with modern surgery alone. They discussed important prognostic, diagnostic, and therapeutic factors including depth of tumor invasion, tumor location, improvements in staging with endorectal ultrasound and magnetic resonance imaging, enhanced surgical technique with total mesorectal excision, circumferential tumor margin, and lymph node dissection that may help to better define a subset of stage II rectal cancer patients in which pelvic radiation may be safely omitted.[17] Moreover, MacKay considered that pre-operative radiotherapy was unnecessary for patients with T1-T3 rectal cancer after TME surgery because of the low local recurrence rate.[18]

In our opinion, if surgical principles can be meticulously kept, pre-operative CCRT might not be necessary for T3N0M0 mid-lower rectal cancer.

## Conclusion

In this study, pre-operative CCRT might not provide better oncological local, distant control or survival benefit for those who have cT3N0M0 middle and low rectal cancer. For a better understanding, a prospective randomized study with a larger number of cases is needed.

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病例分析

# 術前合併化學與放射治療對臨床上第二期初期直腸癌的影響

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**目的**　評估術前合併化學與放射治療對臨床上第二期初期直腸癌的影響。

**方法**　本研究收集自 2000 年 7 月至 2004 年 12 月共 103 位罹患臨床上第二期初期直腸癌的病人資料。其中 37 位病人術前接受核磁共振造影評估腫瘤臨床分期，而另外 66 位病人則接受電腦斷層造影評估之。所有病人中，23 位接受術前合併化學與放射治療，而另外 80 位則否。廣泛性手術切除依照準則而行。最後的分析結果包括存活率、局部復發率以及遠端轉移率。

**結果**　在接受術前合併化學與放射治療的病人族群中，其病理上完全反應率為 34.8%，而降低腫瘤分期率為 73.9%。存活率在兩組病人群中並無顯著差異 (全部病人存活率：91.3% vs. 82.1%；無疾病存活率：86.4% vs. 79.5%；惡性腫瘤相關存活率：91.3 vs. 91.0%)。在局部復發及遠端轉移的控制上也無明顯差異存在。

**結論**　對於罹患臨床上第二期初期直腸癌的病人而言，術前合併化學與放射治療可能沒有提供更好的局部疾病復發控制及存活率。

**關鍵詞**　合併化學與放射治療、核磁共振造影、電腦斷層造影。